Atrius Health Anticoagulation Management Service
CLINICAL GUIDELINE[1] AND PRACTICE PROTOCOL[2]

Authors: Alan Brush, MD, FACP, Peter Collins, PharmD, CACP*, David DeiCicchi, PharmD*, Sandra Elman, PharmD, Ida Gorenburg, MD, Deana Hanna, PharmD*, Mahmoud Moawad, MD, FACP, Aishia Springer, RN, MSN, CACP, Mary Toland, PharmD*, Cheryl Warner, MD
Editors: Harriet Bering, MD*, Mandeep Dhadly, MD*, Damaris Nou, MD*, Andrea Ruby, RN*, Nathan Samuels, NP, DNP, MSN*, Amy Vachon, PharmD*

*Active Contributors as of November 2020

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[1] These guidelines are for informational purposes and are not intended to substitute for the reasonable exercise of independent clinical judgment by providers in a particular set of circumstances of each patient encounter. They are flexible and are intended to be used as a resource for integration with the sound exercise of clinical judgment. They can be used to create an approach to care that is unique to the needs of each patient.

[2] Adapted from the following guidelines and pathways:

1. Antithrombotic and Thrombolytic Therapy, 9th Edition: ACCP Guidelines; vol. 141 supplement CHEST-9) - 2012
2. Kearon, Clive et al; Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. CHEST. February 2016, Vol 149, No. 2
3. European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation – 2018
4. Atrial Fibrillation - European Society of Cardiology - 2016
5. Anticoagulation for valvular heart disease - ACC.AHA-2015
6. Anticoagulation for valvular heart disease - ACC/AHA-2017 focused update
7. ACC Consensus Pathway for Perioperative Management of non-valvular AF - 2017
8. PMAC Online Appendix: Common Procedures and Associated Procedural Bleed Risk
9. American Society of Hematology VTE Guidelines-2018
10. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

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INTRODUCTION

The Atrius Health Anticoagulation Management Service (AMS) is a nurse and clinical pharmacist staffed program that provides comprehensive anticoagulation management services for all oral anticoagulants including warfarin (Coumadin, Jantoven), direct oral anticoagulants (DOACs), and injectable anticoagulants such as subcutaneous unfractionated heparin, low molecular weight heparins, and fondaparinux (Arixtra). This service complements care provided by Atrius Health primary care and specialty clinicians by educating patients, managing anticoagulation therapy, and monitoring adherence and response to therapy.

Atrius Health AMS is designed to improve adherence to evidence-based guidelines by centralizing responsibility for patient monitoring and therapy adjustments regarding anticoagulant medications. This clinical guideline and practice protocol along with the thrombosis collaborative drug therapy management (CDTM) protocol set forth the parameters and protocols followed by the AMS. The patient's primary care physician (PCP) or other treating physician on the patient's care team or coverage system must provide a written order (EpicCare Referral) to enroll a patient in the AMS. By signing this referral, the referring physician is creating an order for the patient to be managed by nurses and clinical pharmacists within AMS under this clinical guideline and practice protocol and the thrombosis CDTM agreement. Only patients whose PCP or applicable specialty physician has signed a referral, indicating agreement with the protocol and CDTM agreement, are eligible for enrollment in the Anticoagulation Management Service.

The AMS is available to all patients who receive their primary care through Atrius Health Internal Medicine practices. Patients are enrolled in AMS by referral from a primary care physician or collaborating prescribing physician who is part of the Atrius Health practices. A patient's PCP or other collaborating or treating physician defines the patient's anticoagulation treatment plan (indication for anticoagulation, treatment goals, and duration of therapy) upon referral to AMS. Once a patient is enrolled and agrees to care under our staff, AMS assumes responsibility for day-to-day management of the enrolled patient's anticoagulation therapy. The service operates 24/7, using an on-call system coordinating with Telecom and the Weekend Urgent Care Program to provide after-hours care. AMS managers coordinate all aspects of anticoagulant management, including interruptions in therapy, and necessary adjustments to anticoagulation therapy. Any deviations beyond the scope of this clinical guideline and practice protocol must be approved by a consultant. For the purpose of this document, a consultant is defined as the patient's PCP or other physician on the patient's care team or covering system, a thrombosis-credentialed CDTM clinical pharmacist, or the AMS Medical Director.

ELIGIBILITY FOR ENROLLMENT

All Atrius PCPs and other participating physicians, as well as their delegates, can currently initiate referrals for management of anticoagulation; all referrals must be approved by a physician. As sites transition to centralized management of DOACs, these clinicians will also be able to initiate referrals for apixaban, rivaroxaban, dabigatran, edoxaban, and betrixaban. AMS may place automatic referrals for patients already taking these medications on behalf of the referring physicians, who will simply need to cosign them.

REFERRAL AND ENROLLMENT

For both Warfarin and DOAC management

- To ensure safe transition of care, clinicians managing patients taking all anticoagulant medications will retain responsibility of prescribing and monitoring these medications until enrollment has occurred.

Patients already on a DOAC:

- **Referral orders:** All physicians in practices undergoing rollout of the DOAC Anticoagulation Management Program will receive an order to cosign REF 195A (REFFERAL TO DOAC ANTI-COAG (aka DOAC) for each of their patients who are currently taking a DOAC.
- **Referral contents:** The referral will include the indication for anticoagulation, currently prescribed DOAC, current dose, duration of therapy, and pertinent labs completed within the past year. AMS will complete the required parts of the referral, including the indication, dose, expected duration of treatment, and supportive information in the event of non-standard indications for using a DOAC.
- Physician agreement: Assuming agreement, the physician will approve the order, which will initiate the enrollment process.
- **AMS Manager completes initial assessment and provides patient education**: Patients already taking DOACs are assumed to have been educated by the prescribing clinician. However, AMS managers will verify each patient's understanding of their DOAC. The patient will not be enrolled into AMS until the AMS manager is able to contact the patient. In the event that the AMS manager is unable to reach the patient for enrollment, a letter will be sent to the referring physician and the patient indicating non-enrollment and offering the patient the opportunity to contact AMS for enrollment. If the patient does not attempt to contact AMS within 1 month of sending this letter, AMS will close the referral.
- **Feedback to referring physician:** The referring physician and the patient's PCP will be notified via Epic message:
    - When a change has been made to DOAC regimen and why (based on insurance, lab values, drug interaction, etc.).
    - When there is a question about the treatment plan or the patient's ability to participate in the program.
    - When AMS staff is unable to contact the patient by phone **within 7 business days** of referral activation, the patient remains under the care of the referring physician until the enrollment process is complete and confirmed. This message will serve as a reminder that the patient has not been enrolled and remains the responsibility of the referring physician. All efforts to contact the patient will be documented in EpicCare.
    - When the patient has been contacted and enrolled.

Patients newly starting a DOAC:

- **Patient agreement:** Prior to referral, the referring physician secures the patient's agreement to participate in the AMS and ensures that the patient is able to meet his/her responsibilities for participation (must be reliably available to receive test results and instructions by telephone, mail, Atrius secure email, or through an identified alternative contact).
- **Initial testing:** Prior to initiating treatment, the referring physician must obtain a baseline hemogram, creatinine and ALT (SGPT) if not done within last 12 months (or creatinine should be done within last 3 months if CrCl <30mL/min), weight, and HCG (if woman in childbearing age) and should assess bleeding risk and fall risk.
- Labs required for enrollment include hemogram, creatinine, ALT (SGPT), and HCG (if woman in childbearing age). AMS staff will order any of these tests in the name of the referring physician when they have not been recently completed per initial testing above. AMS staff may also contact the referring physician to order additional test(s), referencing Appendix 9 for hypercoagulability screening guidelines when this evaluation is needed; the referring physician will be notified of all abnormal results.
- When indicated, clinician should complete a hypercoagulability evaluation (see Appendix 9).
- **Initial dosing:** The referring physician generally starts treatment prior to activating a referral. If assistance is needed to select an appropriate DOAC (including dosing questions), a clinician may send a consult to the DOAC consult pool 109967 (P 109967). The REF 195A (DOAC Anticoagulation referral), SmartRx Atrial Fibrillation and SmartRx Venous Thromboembolism (VTE) Treatment will facilitate clinician DOAC orders.
- **Referral order:** The referring physician completes the DOAC management referral form REF 195A (DOAC Anticoagulation referral), including the prescribed DOAC dosing, indication for oral anticoagulation therapy, anticipated duration of treatment, and other pertinent patient information in the

AMS DOAC Referral. Indications for DOAC referral will be limited to FDA-approved uses of DOAC medications and certain off label indications as indicated on the referral. AMS managers will review all other submitted indications with a consultant prior to enrollment.

- **Basic education:** The referring physician should ideally provide basic education on the effects of specific DOACs, safety issues, reportable symptoms, and the importance of medication adherence. Ideally, the patient should receive appropriate patient education materials at this time. These documents are available in EpicCare as SmartText for After Visit Summary use, or can be included as letters under titles such as **IM* AMS: {DOAC NAME] PATIENT EDUCATION.**
- **AMS Manager completes initial assessment and provides patient education**: The AMS manager will ensure that the patient has received the appropriate education documents. In most cases, AMS will work from the premise that the patient has not yet been educated and therefore provide ALL information that is required for management.
- **Feedback to referring physician:** The referring physician and the patient's PCP will be notified via Epic message:
    - When a change has been made to DOAC regimen and why (based on insurance, lab values, drug interaction, etc.)
    - When there is a question about the treatment plan or the patient's ability to participate in the program
    - When AMS staff is unable to contact the patient by phone **within 7 business days** of receipt of referral, the patient remains under the care of the referring physician until the enrollment process is complete and confirmed. This message will serve as a reminder that the patient has not been enrolled and remains the responsibility of the referring physician. All efforts to contact the patient will be documented in EpicCare.
    - When the patient has been contacted and enrolled.

Patients newly starting on warfarin:

- **Patient agreement:** Prior to referral, the referring physician secures the patient's agreement to participate in the Anticoagulation Management Service and ensures that the patient is able to meet his/her responsibilities for participation. To participate, patients must be reliably available to receive INR results and instructions by telephone, mail, Atrius secure email, or through an identified alternative contact.
- **Initial testing:** Prior to initiating treatment, the referring physician obtains a baseline INR, hemogram and creatinine, if unknown, and HCG (if woman in childbearing age) and assesses for:
    - Risk of bleeding,
    - History of protein C deficiency (which, if present, would necessitate slow start up of warfarin if LMWH is being used), and
    - History of heparin-induced thrombocytopenia.
- If any of the above assessments have not been done, AMS staff may order an INR, hemogram, creatinine and HCG (if woman in childbearing age) in the name of the referring physician or AMS clinical pharmacist credentialed in CDTM for thrombosis. AMS staff may contact the referring physician to order additional test(s) or order these tests directly in the case of an AMS clinical pharmacist credentialed in CDTM for thrombosis, referencing Appendix 9 for hypercoagulability screening guidelines when this evaluation is needed.
    - Note that any baseline INR >1.2 requires the AMS manager to obtain and report to the ordering clinician and PCP the associated prothrombin time/control values (will be provided by the lab on request). This information must be obtained expeditiously; in some cases, anticoagulation may be precluded (i.e., when INR is very high); in all cases, follow-up will need to occur more frequently during startup. Further lab evaluation (which may include liver function tests, anticardiolipin antibody, lupus anticoagulant, and factor levels) should not be delayed, since accurate testing may be precluded once the patient has been fully anticoagulated (see Appendix 9: Hypercoagulability Evaluation).
- **Prior warfarin dosing:** For any patient already on warfarin at the time of referral (e.g., started during a hospitalization or care transferred from an outside physician to Atrius Health), the referring physician is responsible for obtaining most recent INRs and doses to ensure safe transfer of care.
- **Initial dosing:** The referring physician generally starts treatment prior to making a referral. Guidelines for starting anticoagulation therapy are below in Appendix 2: Guideline for Dose Adjustment and Monitoring in New Starts.
- **Basic education:** The referring physician should provide basic education on the effects of warfarin, safety issues, reportable symptoms, and the importance of INR monitoring and provide the patient with appropriate education materials at this time. These documents, including IM* AMS:

Anticoagulation Fact Sheet Insert and IM* AMS: Anticoagulation Fact Sheet Letter, are available as Epic SmartText and letters. In situations when the referring physician has not seen the patient before the referral (e.g., when the patient has been started on anticoagulation during a hospitalization or ER visit), the AMS manager will ensure that the patient receives these documents or similar documents.

- **Documentation:** The referring physician documents the indication for oral anticoagulation therapy, the INR goal, anticipated length of treatment, and other pertinent patient information in the AMS Referral (Type "Ref Anticoag" in EpicCare order window), using specific indications as enumerated in **Appendix 1: Guideline for Establishing INR Goal and Duration of Treatment**.
- **Target ranges:** The AMS operates under an approved guideline (this document), created in accordance with evidence-based anticoagulation literature noted under the first page attributions. Most patients will have indications and target ranges specified in the guidelines. In some patients, however, specific clinical circumstances will require deviations from standard indications and target ranges. These deviations will require review by a consultant on receipt of referral or at any point in the patient's care when target ranges may need to be re-evaluated, must have a basis consistent with a reasonable standard of care, and not be arbitrary or based on the personal preference of the referring physician. No case of this nature will be accepted in the AMS without this review. It is the responsibility of the AMS manager receiving the referral to consult the appropriate consultant, and the responsibility of the consultant to respond on the same business day. Examples of cases that might be considered reasonable though outside of guidelines include:
    - Indication for a higher goal or addition of antiplatelet agent in a patient previously treated at standard goal for atrial fibrillation, then having embolic TIA'S on treatment while in target range.
    - Decrease in goal from high intensity management of 2.5-3.5 to 2.0-3.0 in a patient repeatedly bleeding while in the higher end of this goal range.
- Examples of treatment that would not be considered acceptable include:
    - Use of anticoagulation rather than antiplatelet agents for a patient with PVD without contraindications to antiplatelet agents or without failure of such management and evidence of progressive thromboembolic disease.
    - Use of target ranges including any values below 1.8 for prevention of stroke in patients with atrial fibrillation.
    - Use of a constricted target range such as 2.0-2.2 for management, which is considered impossible to maintain. No treatment range with less than a difference of 0.5 between the high and low end of target range will be accepted.
- **Feedback to referring physician:** The referring physician and the patient's PCP will be notified via Epic message
    - If there is an unresolved question about the treatment plan or the patient's ability to participate in the program.
    - If AMS staff is unable to contact the patient by phone **within one business day** of receipt of referral. The message is a reminder that the patient is not enrolled and therefore not being managed by AMS. All efforts to contact the patient are documented in EpicCare.

For both Warfarin and DOAC management:

- **Hospital discharges:** If the AMS learns of a discharged patient who is on anticoagulation from Case Management, but has not received a referral, the applicable AMS manager will contact the PCP or other appropriate referring specialist (e.g., Cardiology, Orthopedics) to request a referral. Referring physicians are responsible for all applicable requirements listed in warfarin or DOAC referral sections above. Once complete information to facilitate transition of care has been received (including anticoagulant doses and INRs when applicable) and contact is initiated with the patient or designated caregiver by AMS staff and enrollment may occur. When information required to transition care does not arrive until after usual business hours, enrollment may be deferred to the next business day. AMS will not assume the care of the patient, however, in the absence of: (1) a completed referral with all required information and; (2) contact with the patient or designated caregiver. Both are considered indispensable to a safe transition of care.
- **AMS management:** Once enrolled, the AMS will manage all subsequent INRs for warfarin patients and ensure the appropriate dosing and follow up for all anticoagulation patients in accordance with this guideline.

The patient is not enrolled in the Anticoagulation Management Service until the referral has been received, the treatment plan finalized, and the patient contacted by AMS program staff. **The referring clinician retains responsibility for anticoagulation therapy management until notified that the patient has been contacted and is enrolled.**

Anticoagulation Management Responsibilities for Orthopedic Patients Receiving VTE Prophylaxis:

1. **The AMS will assume the responsibility for management of anticoagulation for all patients treated with warfarin or DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) with or without the use of other anticoagulation and antiplatelet therapy. When management only includes other anticoagulants (such as LMWH, fondaparinux, or aspirin), the management remains the responsibility of the orthopedist and/or PCP practice.**
2. **If LMWH or Fondaparinux is used**, the orthopedic surgeon or designee is responsible for arranging for injection, teaching patient or family member or setting up home health services, and writing the prescription.
3. **When warfarin is included in the management plan**, as part or all of VTE prophylaxis related either to the procedure or as continuation of previously ongoing warfarin therapy, AMS will participate in the care and help manage the transition from LMWH or Fondaparinux back to warfarin.
4. **If warfarin is used**, the orthopedic surgeon or designee is responsible for writing the prescription. **2.5mg pills** should be used at time of discharge for all patients, except in unusual circumstances when very high doses (e.g. 10 mg+) or very low doses (<2mg) are being taken at the time of discharge.
5. **If a DOAC is used**, the orthopedic surgeon or designee is responsible for writing the prescription.

Hospital Discharge Procedures for the Orthopedist:

1. When warfarin or DOAC therapy is anticipated, the orthopedist may place a referral to AMS prior to the procedure, noting the expected date of the procedure, the targeted INR range (for warfarin), DOAC medication, and expected duration of therapy. In this case, the orthopedist or designee will need to contact AMS (by Staff Message to the local Anticoagulation pool, accessible by "P Anticoag") after the procedure to trigger activation of the referral and enrollment in AMS. Alternatively, the orthopedist can place this referral following the procedure. In either case, AMS must receive notification and a completed referral by 4pm Monday to Thursday and 3pm on Fridays or enrollment will be deferred to the next business day.
2. Discharge notification must include:
   - Warfarin and/or LMWH/fondaparinux or DOAC dosing in hospital.
   - INR results, if warfarin is being used prior to discharge.
   - Plan for dose on evening of discharge, since patient will generally be advised of this dose at time of discharge.
3. When notification is sent as outlined above, the AMS will assume responsibility for management on the day of discharge.
4. If information is missing or discharge notification is received after 4pm Monday to Thursday and 3pm on Fridays, the AMS will assume responsibility for management on the **next business day,** once complete information has been received.
5. In either case, the AMS manager will notify the orthopedic surgeon at the time of acceptance of the referral. Until that time, the orthopedist remains responsible for management of anticoagulation (including ordering Monday home draws for patients discharged over the weekend).
6. The AMS manager will manage anticoagulation therapy in accordance with the patient's treatment plan and AMS guidelines.

ASSESSMENT AND EDUCATION

FOR DOAC MANAGMENT

INITIAL ASSESSMENT BY AMS MANAGER UPON DOAC REFERRAL

- **Indication**: confirm indication for DOAC therapy. Guidelines are below in Appendix 10. When patient has been referred for a non-approved DOAC indication, a consultant will review referral prior to enrollment.
- **Adherence**: review factors that may affect patient's ability to adhere to therapy (e.g., non-adherence of other medications/medical care)
- **Evaluate if use of DOAC is appropriate** based on:
  - Patient Specific Characteristics (Guidelines are below in Appendix 11)
  - Drug Interactions (Guidelines are below in Appendix 10)
  - For patients in which a DOAC may not be a preferred option based on patient-specific characteristics, or when the chosen DOAC is not appropriate for the patient, the AMS manager should review patient characteristics and issues with a consultant prior to enrollment. When DOAC is inappropriate, AMS manager will directly communicate with the referring physician, and should reference the recommendation of the consultant.
- **Ensure baseline labs/vitals have been obtained:**
  - **Weight within last 12 months**
    - If last weight **(<50kg or >120kg) or BMI >40 kg/m^2, review with a consultant before enrolling in the AMS**
  - **HCG negative** (if woman in childbearing age)
  - **CBC within last 12 months**
    - If hemoglobin < 12.0 or platelet count <100,000, stability of the patient's anemia or thrombocytopenia should be ensured before managing on anticoagulant.
  - **If CrCl >60, serum creatinine within last 12 months (If CrCl 30-60, within last 6 months; if CrCl <30mL/min, within last 3 months)**
    - See Appendix 11 **-** *Anticoagulation Selection Based on Patient Characteristics.* If outside these parameters, review with a consultant before enrolling in the AMS
  - **Calculate Creatinine Clearance (per Cockcroft-Gault)**
  - **Liver function within last 12 months:**
    - No known liver impairment at baseline: ALT (SGPT)
      - If ALT (SGPT) repeatedly elevated >2X ULN, obtain liver function panel to fully assess for liver dysfunction; also order INR (if not already on anticoagulation).
    - Known cirrhosis at baseline: full liver function profile and INR.
      - Child-Pugh Score should be calculated (For Moderate to severe hepatic impairment (Child-Pugh B and C) or liver disease with coagulopathy - See Appendix 11 - *Anticoagulation Selection Based on Patient Characteristics*. If outside these parameters, review with a consultant before enrolling in the AMS
  - **Hypercoagulability work-up, if indicated** (see Appendix 9). If tests are required, the AMS manager will notify clinician
- **Evaluate baseline thrombotic risk** (See Appendix 6)
- **Evaluate baseline bleeding risk** (see Appendix 5)
- **Duration of therapy**: confirm designated duration of therapy in referral is appropriate (see Appendix 1)
  - **Dosing**: confirm current DOAC dose is appropriate or appropriate dose of DOAC to be initiated with consideration to drug interactions (see Appendix 10).

- **Transition**: determine appropriate transition plan to DOAC if patient transitioning from alternative anticoagulant (see Appendix 10).

- **Cost**: ensure patient can afford DOAC and will be able to afford for the duration of therapy (e.g., considering deductibles, co-pays and Medicare donut hole).
- **Indication for PPI**: all patients taking dual anticoagulant-antiplatelet therapy or with a recent upper GI bleed should be taking a PPI in the absence of a contraindication.
    - If patient is a candidate for dual therapy, a recommendation for PPI is communicated to the referring provider.
    - Any standard dose PPI can generally be used depending on presence of drug interactions. For patients on concomitant clopidogrel, pantoprazole may be preferred option
    - **Follow-up**: determine appropriate follow-up interval/monitoring plan for patient (see *Appendix 3: Guidelines for Maintenance Dose Adjustment and Monitoring*.
- **Update patient contact information** as necessary. Patient must provide a working telephone number **and** one or more of the following options:
    - A reliably operating telephone message machine,
    - A reliably functioning cellular phone,
    - An alternate contact designated to receive results and dosing instructions, or
    - Enrollment in MyHealth with agreement to access e-mail regularly for result notification and dosing instructions.

DOAC PATIENT EDUCATION PROVIDED BY AMS MANAGER UPON ENROLLMENT

The AMS manager assesses the patient's understanding of anticoagulation, ensures that patient has received or will receive patient education documents, and provides further instruction on the following topics:

- Reason for taking DOAC (indication) and how DOAC affects clot formation (blocking single clotting factor)
- Length of therapy
- How to administer DOAC (with or without food, etc.)
- How to store DOAC
- If patient previously on warfarin, how DOACs differ from warfarin
    - For example, no INR monitoring required, no need for frequent dose adjustments, no vitamin K interactions, quicker onset/offset of action, likely more expensive
- Brand and generic names for specific DOAC, tablet or capsule, shape/colors/strengths, and importance of verifying tablet strength after each prescription fill/refill
- The requirement for periodic blood tests (CBC, creatinine, ALT), with frequency determined by the AMS guidelines
- The procedure for obtaining blood tests and learning about the results
- The importance of medication adherence and dangers of erratic adherence
- The potential adverse effects of over-anticoagulation (bleeding) and under-anticoagulation (clotting – strokes, systemic emboli, myocardial infarction, DVT, PE or other thromboembolic event for which the patient is receiving anticoagulation)
- Signs/symptoms of bleeding, including intracranial and GI bleeding, and clotting, and what to do if they occur
- Precautionary measures to avoid trauma and bleeding (soft toothbrush, shaver v. razor)
- Drug-drug interactions that can affect DOAC (prescription, over-the-counter)
- Importance of notifying AMS Manager of medication (prescription or OTC), alcohol intake, or other life changes (inability to afford medication)

- Avoidance of contact sports; use of appropriate protection for sports not considered contact sports, but with potential for injuries with falls (e.g., bicycling, skating, skiing)
- Special issues for pregnant/post-partum patients or patients who may be considering pregnancy; risks of anticoagulation during pregnancy
- Importance of making sure that patient has enough of their DOAC medication at all times (refill on time, etc.)
- Medic-Alert necklace/bracelet, medication ID card, or other notification informing other medical caregivers of anticoagulation status
- Need to hold anticoagulation for surgery, colonoscopy, and some other procedures; importance of calling the AMS before any such procedures
- Travel issues, including potential increased vulnerability to DVT/PE during travel (applies to patients with venous thromboembolic risks)
- How to take their DOAC and what to do if doses are missed
- Program operations, including phone number, hours of operation, laboratory testing hours, and other AMS procedures.

All patients enrolled in AMS must verbally contract with the AMS manager to comply with medication advice, testing recommendations, availability for contact after testing, and willingness to communicate all relevant changes in clinical status to the AMS manager. Patients are advised that repeated unavailability to receive results may result in disenrollment from the AMS. In addition, the patient should acknowledge understanding of the risks of under-anticoagulation (increased risk of clotting) and over-anticoagulation (increased risk of bleeding), and agree to avoid potentially risky behaviors.

INITIAL ASSESSMENT BY AMS MANAGER FOR WARFARIN REFERRAL

1. The AMS manager reviews the patient's current medications, relevant medical history, and home or other factors that may affect his/her ability to adhere to therapy.
2. The AMS manager updates patient contact information and contracts for seamless availability to receive dosing instructions on the day of each test. The patient must provide a working telephone number and one or more of the following options:
   - a reliably operating telephone message machine,
   - a reliably functioning cellular phone,
   - an alternate contact designated to receive results and dosing instructions, or
   - Enrollment in MyHealth with agreement to access e-mail regularly for result notification and dosing instructions.

WARFARIN PATIENT EDUCATION PROVIDED BY AMS MANAGER UPON ENROLLMENT

The AMS manager assesses the patient's understanding of anticoagulation, insures that patient has received or will receive the above patient education documents, and provides further instruction on the following topics:

- Reason for taking warfarin (indication)
- Goals of anticoagulation therapy (goal INR, length of therapy)
- Method by which oral anticoagulation is dosed and how this corresponds to the INR value; stress absolute requirement for monitoring, and similarity of warfarin to chemicals used to kill rodents, who are unmonitored when exposed to these chemicals.
- How warfarin affects clot formation
- The brand and generic names for warfarin, tablet sizes/colors/strengths, and importance of verifying tablet strength after each prescription fill/refill

- The requirement for regular blood tests (called prothrombin times, PT-Coumadin tests or INRs) to monitor anticoagulation, with frequency determined by the AMS manager
- The procedure for obtaining an INR test, role of capillary vs. venous testing, learning about the result, and receiving instructions for dosing based on the result
- *The importance of adherence for dosing, testing, and appointments.* ***All patients initially require at least monthly tests, even when clinically stable, with more frequent testing for values out of range, changes in medications that interact with warfarin, intercurrent illnesses (especially those affecting diet and/or GI function), and planned or recent procedures requiring holding of warfarin. Patients with consistently stable values may reasonably defer tests to a maximum of 8 weeks, barring any instances of potential instability, intercurrent illnesses, planned procedures, or changes in medications (see Appendix 3).***
- Patient responsibility for ensuring that he/she is reachable for discussion of results and treatment, as noted above
- The potential adverse effects of over-anticoagulation (bleeding) and under-anticoagulation (clotting – strokes, systemic emboli, myocardial infarction, DVT, PE or other thromboembolic event for which the patient is receiving anticoagulation)
- Signs/symptoms of bleeding and clotting, and what to do if they occur
- How dietary and supplemental vitamin K interacts with anticoagulation; how to safely manage diet
- Common signs of bleeding, and precautionary measures to avoid trauma and bleeding
- Drug-drug interactions that can affect warfarin (prescription, over-the-counter, herbal)
- Use of alcohol during anticoagulation; in general, regular use of alcohol more than one drink daily or episodic use of three or more drinks on any occasion present significant risks of GI bleeding for all patients on warfarin. Episodic or variable use of alcohol creates interactions with warfarin that may significantly increase or decrease INR results, thus presenting additional risks, usually high INRs (over-anticoagulation, thus further risk of bleeding in GI or other sites), less commonly low INRs by increased metabolism of warfarin (under-anticoagulation, thus risk of clotting).
- Importance of notifying AMS Manager of any diet, medication (prescription, over-the-counter, herbal), alcohol intake, other life changes
- Avoidance of contact sports; use of appropriate protection for sports not considered contact sports, but with potential for injuries with falls (e.g., bicycling, skating, skiing)
- Risks of anticoagulation, including intracranial and GI bleeding
- Special issues for pregnant/post-partum patients or patients who may be considering pregnancy; risks of anticoagulation during pregnancy
- Importance of making sure that patient has enough warfarin at all times (refill on time, etc.)
- Medic-Alert necklace/bracelet, medication ID card, or other notification informing other medical caregivers of anticoagulation status
- Need to reverse anticoagulation for surgery, colonoscopy, and some other procedures; importance of calling the AMS before any such procedures
- Travel issues, including potential increased vulnerability to DVT/PE during travel (applies to patients with venous thromboembolic risks) and potential need to obtain testing outside area (all patients, when INR in active management, such as new starts, unstable values, and recent holds)
- How to take warfarin (importance of using evening doses) and what to do if doses are missed [3]
- Program operations, including phone number, hours of operation, laboratory testing hours, notification of INR results, and other AMS procedures.
- Importance of having a bottle of over the counter Vitamin K 100mcg tablets in the home to be used only as directed by AMS staff.

All patients enrolled in AMS must verbally contract with the AMS manager to comply with medication advice, testing recommendations, availability for contact after testing, and willingness to communicate all relevant changes in clinical status to the AMS manager. Patients are advised that repeated unavailability to

[3] If a warfarin dose has been missed, the patient should take the full dose as soon as possible within 12 hours of the missed dose. If more than 12 hours has passed, but it is still before the time of the next planned dose, the patient should take half the prescribed dose, and resume the regular dose at the usual time. If the next dose is already due, the patient should not make up the missed dose, but should contact the anticoagulation manager on the next business day.

receive results and dosing instructions may result in disenrollment from the AMS. In addition, the patient should acknowledge understanding of the risks of under-anticoagulation (increased risk of clotting) and over-anticoagulation (increased risk of bleeding), and agree to avoid potentially risky behaviors.

Pre-Conception Counseling

Patients enrolled in the AMS who are considering pregnancy should receive pre-conception counseling from the Obstetrics service.

Vitamin K in diet and supplements

All patients on warfarin enrolled in the AMS should be advised of the importance of a regular, balanced diet, including green vegetables. When dietary intake cannot be insured, taking a single daily multivitamin containing 10-20mcg of vitamin K will provide some baseline regularity of vitamin K intake. This small addition of vitamin K will not reverse the action of warfarin and may actually help foster more stable INR values in some patients. CHEST-9 recommends against taking additional vitamin K supplement on a regular basis. The availability of this supplement is prudent for all patients, since it provides an option for rapid treatment of markedly elevated INR values, should they occur. When considered, this potential benefit must be balanced against the potential risk of its inappropriate use.

MANAGING NON-ADHERENCE AND OTHER ABSENCES FROM THE PROGRAM

The AMS acts as the designate of the PCP (or other participating physician) in managing the anticoagulation of referred patients in the Atrius Health practices. The PCP retains the medico-legal responsibility for care of these patients, since they are being managed by AMS managers by guideline protocols ordered by the PCP (or other participating physician). When patients are intractably non-compliant, the PCP retains the responsibility for management of this non-compliance, as well. The AMS will make every effort to contact patients overdue for INRs and other lab work (e.g., creatinine, CBC and LFTS when needed) and to obtain cooperation with recommended treatment and follow-up plans. However, when a patient repeatedly fails to return for appropriate follow-up or to comply with treatment recommendations, or for any other reason is deemed unsafe for care by AMS, care may be returned to the PCP.

COMPLIANCE WITH LAB MONITORING FOR ANTICOAGULATION PATIENTS

For patients on warfarin requiring frequent monitoring and are overdue for testing:

- Patients who require frequent monitoring per AMS Operations Manual (e.g., new starts, on enoxaparin or fondaparinux, on hold for high INR, new antibiotic starts, amiodarone starts/tapers or who otherwise require frequent monitoring) are contacted by AMS staff within 24 hours of a missed INR. AMS will attempt to contact the patient during business hours each day until the INR is obtained. At 3-5 days after INR due date, AMS manager will contact the PCP to seek active practice support in engaging the patient in appropriate follow-up care. Continued care by the AMS will depend on the success of this joint effort, and care may be returned to the PCP if patient is unwilling or unable to participate in care.

For patients on warfarin in maintenance phase of care per AMS Operations Manual and are overdue for testing:

- At approximately 1 to 7 days after required lab work due date, patient will receive an automated Televox reminder call and letter via MyHealth (if active).
- At approximately 8 to 14 days after the required lab work due date, patient will receive a second automated Televox reminder call and letter via MyHealth (if active).

- At approximately 22 to 28 days after the required lab work due date, PCP will receive In Basket message and patient will receive a letter mail or MyHealth (if active) stating that they are overdue well beyond safe management standards and need to test within the next 30 days to avoid disenrollment from AMS. The AMS manager may initiate a disenrollment review at this time, though will permit a grace period until 60 days after due date of the test. During this time, steps will include a request for support from the PCP, including an explanation of the potential for disenrollment.
- At approximately 60 days after the INR due date, the patient may be disenrolled from the AMS program with care returned to the PCP. The AMS manager will send a disenrollment letter to the patient and Cc the PCP.

For patients on a DOAC and are overdue for required lab monitoring:

- At approximately 1 weeks after required lab work due date, AMS staff will make an outreach reminder call or send a MyHealth message.
- At approximately 4 weeks after required lab work due date, AMS staff will make an outreach reminder call or send a MyHealth message.
- At approximately 8 weeks after required lab work due date, AMS staff will make an outreach reminder call or send a MyHealth message.
- At approximately 12 weeks, AMS staff will send a letter to inform the patient that he/she is overdue for lab work. This letter will also be cc'd to the patient's PCP so that the PCP (or PCP delegate) can reach out to the patient as a reminder to come in for requested lab work.
- At approximately 24 weeks after the lab work due date, the patient may be disenrolled from the AMS program with care returned to the PCP. The AMS manager will send a disenrollment letter to the patient with the PCP cc'd.

DISCHARGE POLICY FOR ALL ANTICOAGULATION PATIENTS

- For patients who are non-adherent to or no longer have valid indication for anticoagulation therapy, prior to discharging from AMS program, AMS will review with the PCP or other referring physician. This policy encompasses several potential situations:
    1. Patients who had a valid indication for anticoagulation upon referral, but no longer require anticoagulation (e.g., patient with post-operative DVT already completing 3 months of post-DVT diagnosis anticoagulation).
    2. Patients who previously had a valid indication for anticoagulation, but by virtue of change in clinical guidelines, no longer have this indication.
    3. Patients who acknowledge they are no longer taking the anticoagulant, and despite efforts to foster adherence, are not able or willing to comply.
    4. Patients who acknowledge, or it is otherwise demonstrated, that they are not regularly complying with recommended anticoagulation management.
    5. Patients who require lab testing to monitor INRs (when taking warfarin) or other tests required for DOACs, who do not after several requests come to the lab for necessary tests (see Compliance with Lab Monitoring above).
    6. Patients who have had severe complications while taking anticoagulants, such as life-threatening bleeding, and their risk for these events cannot be otherwise mitigated.
- Disenrollment: prior to this process, AMS manager will make every possible effort to work with the patient and members of the patient's primary care team to improve adherence, when that is the issue. This may include, when appropriate, the AMS manager requiring the patient to sign a contract agreeing to the terms of management by the AMS. This written agreement (available as SmartText IM* AMS Contract) must include the signature of the patient and can be signed by either the PCP, AMS manager, or both, as circumstances dictate. It is recognized that the PCP may need the assistance of Case Management or other services to help support the patient's treatment plan. If these collaborative efforts (usually including the adherence contract) prove unsuccessful, the patient may be disenrolled from the AMS.
- Once care has been returned to the PCP, the PCP becomes responsible for discussing any treatment plan changes with the patient. Upon disenrollment, lab results, if any, will go to the PCP's InBasket. If circumstances change and the patient becomes capable and willing to participate in the program and demonstrates regular compliance with PCP management (usually a period of at least 3 months), the PCP can request re-enrollment by sending a new referral to the AMS.

Patients who are managed without AMS involvement for 6 weeks or more (e.g., patients with prolonged hospital or nursing home/rehab facility stays, care by other physicians during winter residence in Florida) may be temporarily disenrolled from the AMS. The PCP or other referring physician can request re-enrollment by re-referral when the patient is ready to return to AMS management. When necessary, AMS managers will assist referring physicians in completing referrals. However, the referring physician remains responsible for providing updated information on recent INR results and warfarin doses and any changes in indication or INR goals.

APPENDIX

Appendix 1: Guideline for Indications, INR goal, Anticoagulant Options and Duration of Treatment (see also, Appendix 10)

- Stroke prophylaxis in the presence of non-valvular atrial fibrillation: either warfarin or the formulary DOACs apixaban (Eliquis) or rivaroxaban (Xarelto) are considered first line agents for most patients, depending on the clinical situation and other non-clinical factors such as insurance coverage and affordability of medication. In general, cost aside, DOACs are favored over warfarin for new starts and patients currently taking warfarin with low time in therapeutic range not related to compliance issues.
- Outpatient VTE treatment in patients without cancer: either enoxaparin (generic Lovenox) + warfarin OR formulary DOACs apixaban (Eliquis) or rivaroxaban (Xarelto) are considered first line agents for most patients.
- VTE prophylaxis after joint replacement therapy: enoxaparin (generic Lovenox) is preferred over other treatments. Warfarin, apixaban and rivaroxaban remain alternative agents currently included in the Atrius formulary.
- Long-term VTE prophylaxis for patients at high risk for recurrence either warfarin or the formulary DOACs apixaban (Eliquis) or rivaroxaban (Xarelto) are considered first line agents for most patients, dependent on the clinical situation and other non-clinical factors such as insurance coverage and affordability of medication.

Indications	Goal INR Range	INR Target	Duration of Therapy/Comments
Prophylaxis of DVT			
• High risk surgery such as joint replacements	See Appendix 8	-	• Options for prophylaxis include LMWH, LDUH, fondaparinux, warfarin, aspirin, and all DOACs; see details in Appendix 8: Anticoagulation Management for Patients Having Orthopedic Surgery.
• High risk patients post-operative patients (obese, bedridden, cancer)	2.0-3.0	2.5	• Until resolution of high-risk condition
• Long distance travel >8 hours, plus additional risk factors for VTE	N/A	N/A	• Single prophylactic dose of LMWH prior to departure
Treatment of DVT (applies to calf, proximal lower extremity or upper extremity) or pulmonary embolism[4]	2.0-3.0	2.5	• *Standard treatment for all indications considered 3 months; extended treatment generally implies lifetime, as long as benefits of anticoagulation exceed bleeding risks, which require yearly reassessment. See footnote below.[5] When DOACs are used, risk of recurrence depends on same factors as warfarin, though effectiveness of treatment is harder to determine.*

[4] Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016; 149:315-352.

			• *Risk of recurrent VTE after stopping treatment depends on (1) efficacy of treatment and (2) patient's intrinsic risk of recurrence. Intrinsic risk depends mostly on presence of provocation for DVT and presence of cancer.* 1. *Risk lower for provocation by surgery (1y: 1%; 5y: 3%) than other factors (estrogen therapy, pregnancy, injury or prolonged travel (1y: 5%, 5y: 15%)* 2. *Risk higher for unprovoked (1y: 10%; 5y: 30%). If cancer present, risk estimated at 15%/year.* 3. *If confined to distal veins, risk about half.* 4. *If recurrent DVT, risk about 50% higher.* ***5.*** *Other factors include:* negative D-dimer testing 1 month after withdrawal of warfarin (risk ratio [RR] 0.4), antiphospholipid antibody (RR 2), hereditary thrombophilia (RR 1.5), male vs female sex (RR1.6), Asian ethnicity (RR 0.8), and residual thrombosis in the proximal veins (RR 1.5). *6.* For all non-cancer patients (where VTE considered cancer-related), all current guidelines prefer DOACs to warfarin, and warfarin to LMWH. However, other factors such as patient cost and patient preference may alter this hierarchy. These comments apply to all indications for treatment and prophylaxis of DVT listed in this Appendix. Refer to *Appendix 4: Guideline for Initial Outpatient Treatment of Venous Thrombosis and Pulmonary Embolus* for details of treatment of VTE with all agents. *7.* Rivaroxaban, apixaban, dabigatran, and edoxaban are FDA approved for this indication, but only rivaroxaban and apixaban are currently on the Atrius formulary. All subsequent comments in this Appendix refer to use of DOACs on formulary. More complete information can be found in *Appendix 10: apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), and rivaroxaban (Xarelto) and Appendix 11: Considerations for Anticoagulant Selection in Atrial Fibrillation and VTE Treatment***.**
• Patients with high clinical suspicion of DVT/ PE awaiting diagnostic testing	N/A	N/A	• Begin treatment immediately with agent for initial therapy (see below). We recommend a

			single injection of LMWH or appropriate DOAC while awaiting results, regardless of presence of DOACs on formulary. Both apixaban and rivaroxaban are immediately effective and do not require initial systemic treatments.
• Patients with intermediate clinical suspicion of DVT/ PE awaiting diagnostic testing	N/A	N/A	• If results are expected to be delayed >4 hours, begin treatment immediately with agent for initial therapy, as above.
• 1st episode of DVT/PE due to transient, reversible identifiable risk factor	2.0-3.0	2.5	• Option 1: Weight-based SC LMWH, weight-based unmonitored SC UFH, or SC fondaparinux for at least 5 days **and** until INR is ≥2.0 at least 24 hours; warfarin should be started on day of initial treatment. • Option 2: Begin treatment with DOAC. Both apixaban and rivaroxaban are immediately effective and do not require initial systemic treatments. They can be used in all circumstances listed below, including the presence of active cancer and active cancer treatment. • 3 months is recommended duration of treatment if identified underlying condition is already resolved or >3 months when underlying condition not yet resolved.
• 1st episode, high risk of recurrent thrombosis due to identifiable risk factor that is likely to persist	2.0-3.0	2.5	• Option 1 or 2 as noted above. • Treatment duration indefinite, as long as identifiable risk factor persists
• 1st episode, patients with DVT/PE and active (clinically active and/or in active treatment) cancer	2.0-3.0	2.5	• Based on 2018 International Initiative on Thrombosis and Cancer (ISTH) Guidance[120], the 2019 American Society of Clinical Oncology Guideline[121], and the 2019 International Initiative on Thrombosis and Cancer (ITAC) Guideline[122] generally recommend use o:f LMWH or specific DOACs as preferred therapies for VTE treatment in cancer patients. In setting of low bleeding risk and no-drug-drug interactions, DOACs may be preferred, while LMWH may be preferred in the setting of high risk of bleeding • If using warfarin, same considerations as noted in above box apply. Continue duration until oncologist considers patient no longer at risk.
• 1st episode without identifiable cause	2.0-3.0	2.5	• Option 1 or 2 as noted above. • 3 months (minimum duration) followed by risk benefit evaluation for long-term therapy. Considerations:

1. If first VTE is distal with no PE, 3 months usually sufficient for all bleeding risks. Alternatively In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, can consider serial imaging of the deep veins for 2 weeks over anticoagulation.[6]
2. If first episode of VTE that is a proximal DVT or PE, extended treatment suggested for low or moderate bleeding risk; 3 months recommended for high bleeding risk.
3. If second such episode, long-term treatment recommended (after same assessment) unless bleeding risk is high.

- If patient is receiving long-term treatment, periodic (at least yearly) risk-benefit reassessment should occur. Long-term treatment should be at same intensity INR as initial treatment, goal range 2.0-3.0. Lower intensity (1.5-1.9) is not recommended except on a case-by-case basis and only instead of no long-term treatment, which may occur when there is significant patient concern about bleeding or preference for less frequent monitoring. In any case, it should never occur until at least 3 months of standard intensity treatment.[7] [8] Note: decrease in bleeding risk at lower intensity of anticoagulation has not clearly been demonstrated, and preventive efficacy is modestly decreased compared to standard intensity treatment. When treatment is long-term, use of initial treatment agents recommended, either warfarin or DOACs. Warfarin can be used at standard treatment doses. See Appendices 4, 10, or 11 for DOAC dosing.

[6] Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016; 149:315-352.

[7] An elevated D-Dimer result one month after cessation of anticoagulation is highly predictive of an increased risk of recurrence. Therefore, we recommend checking D-Dimer in patients with idiopathic DVT who have discontinued warfarin after the acute treatment phase. If high, we recommend reinstitution of prophylactic anticoagulation for up to 4 years. Palaretti, Gaultieor et al. D-Dimer Testing to Determine the Duration of Anticoagulant Therapy. NEJM; 2006; 355(17): 1780-9. http://content.nejm.org/cgi/content/abstract/355/17/1780

[8] "The results of extended-duration therapy reflect follow-up only to 4 years; the risk-benefit ratio is not known for longer durations. Clinicians should weigh the benefits, harms and patient preferences in deciding on the duration of anticoagulation." Any duration longer than 4 years should include a decision by the patient and treating physician, including the understanding that evidence for longer durations of treatment does not yet exist. Snow, Vincenza et al. Management of Venous Thromboembolism: A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians. Annals Intern Med. 2007; 14(5): 204-210. http://www.annals.org/cgi/content/full/146/3/204

• 1st episode, high risk of recurrent thrombosis due to identifiable risk factor likely to persist	2.0-3.0	2.5	• Option 1 or 2 as noted above • Lifetime; unless high-risk condition resolves (at least 3 months). LMWH provides a safe and effective alternative for these patients, and may be preferable for patients with cancer or for patients with difficult to control INR results.[9] When treatment is long-term for non-cancer diagnosis, see above regarding choice of agents.
• 2nd episode, whether or not cause identifiable, if cause unknown or not resolved	2.0-3.0	2.5	• Option 1 or 2 as above • Lifetime warfarin (standard intensity 2.0-3.0 recommended for low bleeding risk and suggested for moderate bleeding risk, or use DOAC at recommended dose for secondary prevention; 3 months suggested for high bleeding risk. Note that low intensity 1.5-2.0 goal is not recommended; however, this option may be considered in the presence of increased bleeding risk and/or patient preference **after 12 months** at standard intensity when the only other option is discontinuation of anticoagulation. Note: decrease in bleeding risk at lower intensity of anticoagulation has not clearly been demonstrated, and preventive efficacy is modestly decreased). When treatment is long-term, use of initial treatment agents recommended, either warfarin or DOACs. Warfarin can be used at standard treatment doses. See Appendix 4 or Appendix 10 for DOAC dosing.
• Asymptomatic DVT (unexpected finding or serendipitously discovered) should be evaluated, treated initially and subsequently in the same way as symptomatic DVT/PE	2.0-3.0	2.5	• Use relevant criteria from above boxes.
• Superficial vein thrombosis (SVT) of at least 5cm length	N/A	N/A	Prophylactic fondaparinux or LMWH for 45 days preferred over no treatment. Fondaparinux suggested over LMWH. Rivaroxaban 10 mg daily may also be considered, since non-inferior to fondaparinux.[10]
• Superficial vein thrombosis (SVT) of less than 5cm length	2.0-3.0	2.5	• Anticoagulation may be considered if

[9] Snow, Vincenza et al. Management of Venous Thromboembolism: A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians. Annals Intern Med. 2007; 146(5): 204-210

[10] Beyer-Westendorf, Jan et al; Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomized, non-inferiority SURPRISE phase 3b trial; Lancet Haematol 2017; 4: e105–13; published online February 15, 2017

• Upper extremity DVT (involving axillary or more proximal veins)			○ thrombosis is recurrent, ○ clot occurs within 5 cm of the deep vein system ○ clot occurs in the superficial saphenous vein, or ○ patient has systemic risk factors that increase risk for clots. • In these circumstances, prophylactic fondaparinux or LMWH for 45 days preferred over no treatment. Fondaparinux suggested over LMWH. Rivaroxaban 10 mg daily may also be considered, since non-inferior to fondaparinux.[11] When endovascular ablation occurs, further anticoagulation may not be required. Consult vascular surgeon when questions arise. Considerations: • Treatment protocol same as lower extremity DVT, using initial LMWH, IV UFH, or fondaparinux with 24-hour overlap at therapeutic INR with warfarin, or DOAC continued for no less than 3 months, assuming VTE not cancer-related. When cancer-related, LMWH (or fondaparinux when LMWH contraindicated or otherwise inappropriate for patient) preferred. • If DVT associated with IV catheter and catheter still present and functioning, it does not need to be removed; continued anticoagulation recommended for patients with cancer and suggested in patients with no cancer. • If DVT associated with IV catheter and catheter removed, treatment recommended for 3 months. • Routine use of compression stockings or wraps not recommended unless at specific high risk for swelling.
• **Splanchnic (portal, mesenteric, or splenic) or hepatic vein thrombosis**	2.0-3.0	2.5	• Treat only if symptomatic, not if incidentally detected.
• **DVT/PE while at therapeutic level of anticoagulation, without identifiable cause or with identifiable cause likely to persist**	2.5-3.5, or as indicated by INR at time of event	3.0, or as indicated by INR at time of event	• Treatment with LMWH at least a month, with consideration of indefinite use. Consider patient non-compliance and evaluation for underlying malignancy when VTE truly recurrent. Consider filter when at high risk for

[11] Ibid

			life-threatening PE, when higher level of anticoagulation is precluded, and/or when event occurred at high end of therapeutic range.[12]
• **DVT/PE while at therapeutic level of anticoagulation, with identifiable cause no longer present**	2.5-3.5, or as indicated by INR at time of event	3.0, or as indicated by INR at time of event	• At least 12 months with warfarin or DOACs, and in addition consider temporary use of LMWH, as above, without use of IVC filter; consider filter when at high risk for life-threatening PE, when higher level of anticoagulation is precluded, and/or when event occurred at high end of therapeutic range.
• **Prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding**	N/A	N/A	• Betrixaban or rivaroxaban (see Appendix 10)
Thrombophilias and DVT[13]			
a. **1st or subsequent episode in the presence of high risk thrombophilia**, defined as: b. One spontaneous event plus antiphospholipid syndrome, deficiency of anti-thrombin, protein C, or protein S, or multiple abnormalities c. Two or more spontaneous events plus any other cause of thrombophilia d. One spontaneous life threatening event, such as massive near fatal PE, cerebral, mesenteric or portal vein thrombosis e. One spontaneous event at unusual site, such as cerebral, mesenteric or portal vein regardless of presence of genetic factor for thrombophilia, in the absence of a provoking cause that has resolved f. One spontaneous event in usual site, such as DVT/PE, in setting of more than one genetic factor for thrombophilia	2.0-3.0	2.5	• Lifetime (standard intensity 2.0-3.0); treatment phase 3 months and then prophylactic phase for lifetime (standard intensity unless clinical circumstances indicate otherwise). • DOACs can replace use of warfarin in most circumstances of thrombophilia. In antiphospholipid syndrome, warfarin is currently preferred, as studies supporting effectiveness of prevention with DOACs have not yet been completed.
• **Lupus inhibitor with other risk factors or thromboembolic events while at therapeutic INR**	2.5-3.5	3.0	Lifetime
• **Other inherited thrombophilias (see Appendix 9)**	2.0-3.0	2.5	• Initial treatment 3 months; lifetime prophylaxis preferred, as in DVT/PE without identifiable cause, but mandatory only if 2 or more spontaneous thromboses, • One spontaneous life-threatening thrombosis or thrombosis at unusual site, • One spontaneous thrombosis in presence of >1 high-risk genetic defect.
Acute Myocardial infarction and LV thrombus or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality)			• DOACs are not recommended in any of these situations:

[12] Kearon, Clive et al; Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. CHEST. February 2016, Vol 149, No. 2; 345

[13] Makris, M; Thrombophilia: Grading the Risk; Blood May 21, 2009 vol. 113 no. 21 5038-5039

• ->with no stenting	2.0-3.0 (3 months)	2.5 (3 months)	• Warfarin plus low-dose aspirin 75 to 100 mg daily recommended over single antiplatelet therapy or dual antiplatelet therapy for the first 3 months. Thereafter, discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months recommended as in ACS. After 12 months, single antiplatelet therapy recommended as in established CAD.
• ->with BMS placement	2.0-3.0 (3 months	2.5 (3 months)	• ACS therapy (warfarin, low-dose aspirin, clopidogrel 75 mg daily) for 1 month suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the 2nd and 3rd month post-BMS suggested over alternative regimens/time frames for warfarin use. Thereafter, discontinuation of warfarin and use of dual antiplatelet therapy for up to 12 months recommended as in ACS. After 12 months, single antiplatelet therapy recommended as in established CAD.
• ->with DES placement	2.0-3.0 (3-6 months)	2.5 (3-6 months)	• Triple therapy (warfarin, low-dose aspirin, clopidogrel 75 mg daily) for 3 to 6 months suggested over alternative regimens/durations of warfarin therapy. Thereafter, discontinuation of warfarin and continuation of dual antiplatelet therapy for up to 12 months recommended as in ACS. After 12 months, antiplatelet therapy recommended as in established CAD.
LV Dysfunction without evidence of CAD			
• ->with no evidence of LV thrombus	-- 2.0-3.0 if warfarin used	-- 2.5 If warfarin used	• Combination of antiplatelet agents and anticoagulation with warfarin is not recommended. • When compared in patients with decreased LV function, there was no significant difference between warfarin and aspirin in primary outcomes of death or stroke. In patients studied for 4 or more years, there may have been a small benefit for patients on warfarin vs aspirin. However, in general, any benefit offset by the higher risk of hemorrhage in patients on warfarin.[14]
• ->with identified acute LV thrombus (e.g. Takotsubo cardiomyopathy)	2.0-3.0 (3+ months)	2.5 (3+ months)	• Anticoagulation with warfarin at least 3 months suggested.
Stable coronary artery disease or peripheral artery disease (prevention of major cardiovascular events)	N/A	N/A	• Rivaroxaban 2.5 mg twice daily; administer in combination with daily low dose aspirin.

[14] Warfarin and aspirin in patients with heart failure and sinus rhythm. Homma S, et al, WARCEF Investigators; N Engl J Med. 2012; 366(20):1859.

Atrial fibrillation with stable CAD	2.0-3.0	2.5	• For patients with AF and stable coronary artery disease (e.g., no acute coronary syndrome within the previous year) and who choose oral anticoagulation, we suggest OAC with either a DOAC • or adjusted dose warfarin therapy alone rather than the combination of OAC and aspirin (CHEST-2018)

Atrial Fibrillation (AF) without valvular disease (includes paroxysmal and chronic AF and Atrial Flutter)[15]			• In patients with AF who are eligible for OAC, DOACs recommended over warfarin (CHEST-2018). This recommendation applies to all atrial fibrillation patients in the absence of valvular AF (AHA/ACC/HRS-2019).
			• For patients with AF about to begin anticoagulation, SAMe-TT2R2 score recommended to aid decision-making to help identify patients likely to do well on warfarin.
			  • 0-2: likely to achieve reasonable TTR.
			  • >2; likely to require more regular INR checks, education/counseling, and frequent follow-up. Assuming high medication adherence, DOACS should be considered (CHEST-2018).
			For patients with AF (except valvular AF) who are unable to maintain a therapeutic INR, level with warfarin, use of a DOAC is recommended (AHA/ACC/HRS-2019).

• **Low risk for ischemic stroke, TIA or systemic embolism: lone AF/flutter** (no risk factors, age<65, and no clinical or echocardiographic evidence of cardiomyopathy or valvulara disease); CHA2DS2-VASc = 0 (or CHA2DS2-VASc = 1 for women per 2016 ESC guideline) • **see Appendix 6 for CHA2DS2-VASc risk score assessment**	N/A	N/A	• 2014 ACC/AHA/HOURS, 2016 ESC and CHEST-2018 guidelines suggest against treatment with aspirin or anticoagulation.
• **Intermediate risk for ischemic stroke, TIA or systemic embolism: AF/flutter with one moderate risk factor,** either diabetes, hypertension, moderate to poor systolic function), age 65-74, age ≥75, vascular disease, or female sex; CHA2DS2-VASc = 1 (or CHA2DS2-VASc = 2 for women per 2016 ESC guideline) • **see Appendix 6 for CHA2DS2-VASc risk score assessment**	2.0-3.0 if warfarin	2.5 if warfarin	• 2014 AHA/ACC/HOURS: For patients with CHA2DS2-VASc score =1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered. • 2016 ESC and CHEST-2018: For men with CHA2DS2-VASc score = 1 and women with CHA2DS2-VASc score = 2, warfarin or DOAC should be considered, taking into account individual characteristics and patient preferences (note: antiplatelet therapy not recommended). In setting of AF/flutter without valvular heart disease, for all levels of risk for

[15] All comments refer to persistent or paroxysmal AF/flutter, not to single episode due to reversible cause such as acute pulmonary infection.

			TIA, stroke or systemic embolism, anticoagulation with DOACs preferred to warfarin. Choice of oral anticoagulation is based on patient characteristics and preferences.
• **High risk for ischemic stroke, TIA or systemic embolism: AF/flutter with history of previous TIA, ischemic stroke, or systemic embolism <u>OR</u> two or more moderate risk factors**, including diabetes, hypertension, moderate to poor systolic function, age 65-74, age ≥75, vascular disease, or female sex; CHA2DS2-VASc of 2 or more (CHA2DS2-VASc of 3 or more in women per 2016 ESC guideline) • **see Appendix 6 for CHA2DS2-VASc risk score assessment**	2.0-3.0 if warfarin	2.5 if warfarin	• Lifetime; either warfarin or DOACs depending on patient specific characteristics.
• **AF/flutter managed with rhythm control**			• 2014 AHA/ACC/HOURS and 2016 ESC guidelines suggest antithrombotic therapy for atrial flutter follow same principles as atrial fibrillation.
• **AF/flutter with native rheumatic mitral valve disease**	2.0-3.0	2.5	• Lifetime oral anticoagulation recommended; if rheumatic mitral stenosis, DOACS not recommended.
• **AF/flutter with bioprosthetic mitral and/or aortic heart valve**	2.0-3.0	2.5	• Lifetime; <u>consider</u> addition of aspirin 81 mg, especially in presence of atherosclerotic vascular disease, unless patient at high risk of bleeding, such as in patients with history of GI bleed or >80 years of age. DOACs acceptable > 3 months post-operatively if for degenerative mitral regurgitation or in the aortic position.[16]
• **AF/flutter with mitral stenosis**	2.0-3.0	2.5	• Lifetime; if unable to take warfarin for any other reason than bleeding, dual antiplatelet therapy recommended over aspirin alone. DOACS not recommended.
Atrial Fibrillation/flutter, <u>duration of at least 48 hours or unknown</u>, with planned electrical or pharmacologic cardioversion			
• **Option 1**	2.0-3.0	2.5	• LMWH, DOAC, or warfarin at full therapeutic range for at least three consecutive weeks. If using warfarin, INR must be at least 2.0 for 3 consecutive weeks preceding cardioversion and below 4.2 on day of cardioversion. During this period, the goal will remain 2.0-3.0, but the AMS manager will attempt to keep the INR in the 2.5-3.0 range. If ANY value falls below 2.0, the AMS manager will notify the cardiologist, so the patient's procedure can be postponed.[17]

[16] The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

[17] Assuming INR at least 2.0 for 3 weeks:

			• Post-cardioversion, patient requires at least four weeks of therapeutic anticoagulation with warfarin or DOAC regardless of risk factors
• **Option 2**	2.0-3.0	2.5	• IV UFH with target PTT of 60 (range 50-70s), LMWH in therapeutic doses, DOAC for at least 24 hours, or at least 5 days of warfarin with target INR 2.5 (range 2.0-3.0) and TEE showing no clot prior to cardioversion (decision made during hospitalization). • Use Option 1 if clot found at time of cardioversion, and repeat TEE prior to attempting later cardioversion. Post-cardioversion, patient requires at least four weeks of anticoagulation in this range regardless of risk factors; longer duration is based on whether patient has had >1 prior episode of AF, and risk factor status.
Atrial Fibrillation/flutter, duration <48 hours, with planned electrical or pharmacologic cardioversion (also applies to emergency cardioversion with atrial fibrillation/flutter of any duration)			
• **Option 1**	2.0-2.5	2.5	• Immediate cardioversion without preceding anticoagulation (decision made on presentation or during hospitalization). 2014 ACC/AHA Guidelines recommend heparin, LMWH, or DOAC as soon as possible prior to cardioversion, especially if previous thromboembolism, CHF or DM present, but can be omitted in lower risk patients. ESCAF 2016 recommends this anticoagulation for all patients. • Anticoagulation with an oral anticoagulant recommended for at least 4 weeks after successful cardioversion, regardless of baseline stroke risk.
• **Option 2**	2.0-3.0	2.5	**P**referred if no contraindication to anticoagulation)**:** • Begin LMWH or UFH immediately (decision made during hospitalization) and then proceed to cardioversion; if patient is clinically unstable and requires urgent cardioversion, anticoagulation should not delay cardioversion.

- CV will be performed at INR <4.2
- CV will be postponed if INR >5.0 – AMS manager will notify cardiologist to coordinate plan
- Cardiologist will make case-by-case decision for INR in range 4.2-5.0.

* Note that the AHA/ACC 2017 Focused Update of the 2014 Guidelines for Management of Mechanical Heart Valves only comments that it is "reasonable" to use the 1.5-2.0 range for patients without thromboembolic risk factors. The decision to use this range requires the specific recommendation of the cardiologist and/or thoracic surgeon. Nishimura, R et.al; 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease of Patients With Valvular Heart Disease; Circulation. 2017;135: page e1174

			• Continue anticoagulation with warfarin at least 4 weeks after cardioversion regardless of risk factors.
Atrial Fibrillation with ACS			• For patients with ACS and AF at increased risk of systemic thromboembolism (CHA2DS2-VASc ≥2), anticoagulation is recommended unless the bleeding risk exceeds the expected benefit (AHA/ACC/HRS-2019).
Atrial fibrillation patients requiring Oral Anticoagulant (OAC) undergoing elective PCI/stenting (Whenever triple therapy is considered, must weigh bleeding and thrombotic risks (CHEST-2018)			• Low bleed risk (HAS-BLED 0-2): triple therapy for 1-3 months followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, then OAC monotherapy. • High Bleed risk (HAS-BLED ≥3): triple therapy for 1 month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, then OAC monotherapy. • Unusually high bleed risk (HAS-BLED ≥3 and/or recent acute bleeding event) and low thrombotic risk: OAC plus single antiplatelet (preferably clopidogrel) for 6 months, then OAC monotherapy. (CHEST-2018)
Atrial fibrillation patients requiring Oral Anticoagulant (OAC) presenting with an ACS, undergoing PCI/stenting (Whenever triple therapy is considered, must weigh bleeding and thrombotic risks (CHEST-2018)			Both CHEST-2018 and AHA/ACC/HRS-2019 present reasonable options, and may be chosen by the clinician managing the patient. **CHEST-2018 recommendations:** • Low bleed risk (HAS-BLED 0-2) relative to risk for ACS or stent thrombosis: triple therapy for 6 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, then OAC monotherapy • High bleed risk (HAS-BLED ≥3): triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, then OAC monotherapy. • Unusually high Bleed risk (HAS-BLED ≥3 and/or acute bleeding event) and low thrombotic risk: OAC plus single antiplatelet (preferably clopidogrel) for 6-9 months, then OAC monotherapy **AHA/ACC/HRS-2019 recommendations:** • In patients with AF at increased risk of stroke (CHA2DS2-VASc ≥2) who have undergone PCI with stenting for ACS, double therapy with

			a P2Y12 inhibitor (clopidogrel or ticagrelor) and dose-adjusted vitamin K antagonist, clopidogrel and low-dose rivaroxaban 15 mg daily, or clopidogrel and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding as compared with triple therapy (• If triple therapy is prescribed for patients with AF at increased risk of stroke/systemic thromboembolism (CHA2DS2-VASc ≥2) who have undergone PCI with stenting for ACS, clopidogrel in preferred over prasugrel**.** • If triple therapy is prescribed for patients with AF who are at increased risk of stroke/systemic thromboembolism (CHA2DS2-VASc ≥2) and who have undergone PCI with stenting for ACS, a transition to double therapy (oral anticoagulant and P2Y12 inhibitor) at 4 to 6 weeks may be considered.
Bioprosthetic (tissue) heart valves, during first three months, no AF or history of systemic embolus.	2.0-3.0	2.5	• ACC/AHA 2017 recommends anticoagulation with an INR target of 2.5 may be reasonable for at least 3 months and perhaps for as long as 6 months after implantation of a surgical bioprosthetic MVR or AVR[18]. •
• **All bioprosthetic (tissue) heart valves, during the first three months post replacement, no AF but with history of systemic embolus prior to valve replacement**	2.0-3.0	2.5	• Anticoagulation with warfarin for 3 months after valve replacement; then reassess based on other clinical issues noted above
• **All bioprosthetic (tissue) heart valves, after first three months, no AF or history of systemic embolus**	N/A	N/A	• Aspirin 81 mg
• **All bioprosthetic (tissue) heart valve + AF**	2.0-3.0	2.5	• Lifetime standard dosing warfarin; consider addition of aspirin 81 mg, especially in presence of atherosclerotic vascular disease, unless patient is at high risk of bleeding, such as in patients with history of GI bleed or >80 years of age. DOACs acceptable > 3 months post-operatively if for degenerative mitral regurgitation or in the aortic position.[19]
• **All bioprosthetic (tissue) heart valve plus LV dysfunction, pacemaker, large LA, embolic stroke, or hypercoagulable state**	2.0-3.0	2.5	• Lifetime
• **TAVR**	2.0-3.0	2.5	• Anticoagulation with warfarin to achieve an INR of 2.5 reasonable for at least 3 months after TAVR in patients at low risk of bleeding; this

[18] Anticoagulation for valvular heart disease - ACC/AHA-2017 focused update; page 26
[19] The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

			intervention, compared with ASA alone, decreases risk of valve thrombosis[20]
Mechanical heart valves – following placement all initially require bridging with LMWH or UFH until INR stable in therapeutic range. If UFH, prophylactic dose; if LMWH, may be prophylactic or treatment dose. See *Arterial Thromboembolic Risk Assessment*.	2.0-3.0	2.5	• All require bridging with LMWH or UFH until INR stable in therapeutic range. If UFH, use prophylactic dose; if LMWH, may be prophylactic or treatment dose. • Aspirin 81 mg should be added to long term treatment of all valves for all patients based on their individual bleed risk (note: age is not an automatic exclusion in ACC/AHA or CHEST-2012, only recent GI bleeding). Note 65% risk reduction in major systemic embolism or death when aspirin is added to warfarin.
• **Aortic mechanical valves + no other risk factors** ○ On-X AVR and no thromboembolic risk factors ○ Low risk (low thrombogenicity) valves *plus* normal sized atrium: bileaflet valves (St. Jude, Carbomedics) and tilting disc valves (Medtronic Hall tilting disc) ○ Higher risk (higher thrombogenicity) valves: other tilting disk valves (Bjork-Shiley, Monostrut, Omnicience/Omnicarbon, Ultracor) and caged ball valves (Starr-Edwards)	1.5-2.0 2.0-3.0 2.5-3.5	1.75 2.5 3.0	• Lifetime warfarin plus low dose ASA after initial 3-month period of standard 2.0-3.0 target range – see above[21] • Lifetime warfarin plus low dose ASA – see above. • Add aspirin 81 mg to high-intensity anticoagulation for lifetime if patient at low risk of bleeding, avoid in patients with history of GI bleed or >80 years of age.
• **All mechanical valves (except On-X aortic mechanical valve) + risk factors, including** AF, LV dysfunction, anterior-apical ST-segment elevation MI, LAE, low EF, or hypercoagulable state	2.5-3.5 + aspirin 81mg daily	3.0	• Add aspirin 81 mg to high-intensity anticoagulation for lifetime, unless patient at high risk of bleeding, such as in patients with history of GI bleed or >80 years of age. • Lifetime. DOACs not recommended.
• **On-X mechanical aortic valve + risk factors, including above risk factors but excluding** right-sided valve replacement, mitral valve replacement, double (aorta plus mitral) valve replacement, patients with active endocarditis at implantation, previous confirmed or suspected thromboembolic event or thrombophlebitis occurring or resolving within the last year prior to enrollment, and patients who are in an emergency state.[22]	2.0-3.0 (or 1.5-2.0 at the discretion of the cardiologist and/or thoracic surgeon) + Aspirin 81 mg daily	2.5 (or 1.75 at discretion of cardiologist and/or thoracic surgeon) + Aspirin 81 mg daily	• Lifetime; if patient at low risk of bleeding, add aspirin 81 mg to high-intensity anticoagulation for lifetime; avoid in patients with history of GI bleed or >80 years of age. • If using 1.5-2.0 option, must use aspirin 81 mg as well.
• **Mitral mechanical valves: all types considered higher thrombogenicity**	2.5-3.5	3.0	• Lifetime; if patient at low risk of bleeding, add aspirin 81 mg to high-intensity anticoagulation

[20] Anticoagulation for valvular heart disease - ACC/AHA-2017 focused update; page 27
[21] Anticoagulation for valvular heart disease - ACC/AHA-2017 focused update; page 27
[22] Note that the AHA/ACC 2017 Focused Update of the 2014 Guidelines for Management of Mechanical Heart Valves only comments that it is "reasonable" to use the 1.5-2.0 range for patients without thromboembolic risk factors. The decision to use this range requires the specific recommendation of the cardiologist and/or thoracic surgeon. Nishimura, R et.al; 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease of Patients With Valvular Heart Disease; Circulation. 2017;135: page e1174

			for lifetime; avoid in patients with history of GI bleed or >80 years of age.
Valvular heart disease, all native valves			
• **Mitral stenosis/insufficiency (rheumatic) with NSR and LA <5.5 cm**	N/A	N/A	• No anticoagulation or antiplatelet agents
• **Mitral stenosis/insufficiency (rheumatic) with NSR and LA ≥5.5 cm**	2.0-3.0	2.5	• Lifetime
• **Mitral stenosis/insufficiency (rheumatic) with AF. previous systemic embolism, or left atrial thrombus**	2.0-3.0	2.5	• Lifetime; do not use concomitant anti-platelet agents unless systemic embolus at therapeutic INR
• **Mitral stenosis/insufficiency (rheumatic) with AF or history of systemic embolism while on oral anticoagulant at therapeutic range**	2.0-3.0	2.5	• Lifetime; add aspirin 81 mg or consider increase INR target range to 2.5-3.5.
• **Mitral valve disease and planned percutaneous valvotomy (PMBV) with LA thrombus present**	2.5.3.5	3.0	• Pre-procedural TEE to exclude LA thrombus; if thrombus found, anticoagulate with warfarin until TEE documents resolution; do not perform procedure until thrombus resolved.
• **Mitral valve prolapse (MVP) without associated risk**	N/A	N/A	• No anticoagulation or antiplatelet agents indicated
• **Aortic mechanical valves plus risk factors (atrial fibrillation, prior thromboembolism, left ventricular dysfunction, or hypercoagulable states)** • **All mitral mechanical valves**	2.5-3.5	3.0	• Lifetime higher intensity warfarin plus low dose ASA, unless high bleed risk.
• **All mechanical valves + history of systemic embolus despite a therapeutic INR**	See comment		• Add aspirin 81 mg to anticoagulation for lifetime, and/or or increase intensity of INR goal 0.5 above prior goal range. • If previously 2.0-3.0, increase to 2.5-3.5; if previously 2.5-3.5, increase to 3.0-4.0.
• **MVP with history of TIA or stroke**	N/A	N/A	• Aspirin 81 mg daily
• **Mitral valve repair in normal sinus rhythm, first three months**	N/A	N/A	• Aspirin 81 mg daily
• **MVP with AF, documented systemic embolism, or recurrent TIAs despite aspirin therapy**	2.0-3.0	2.5	• Lifetime
• **Mitral annular calcification (MAC) with no AF complicated by systemic embolism or TIA**	N/A	N/A	• Aspirin 81 mg daily. Consider warfarin if recurrent symptoms while on aspirin.
• **Mitral annular calcification with AF**	2.0-3.0	2.5	• Lifetime
• **Aortic stenosis/insufficiency in normal sinus rhythm**	N/A	N/A	• No anticoagulation or antiplatelet agents indicated
• **Aortic valve disease with annular calcification in normal sinus rhythm**	N/A	N/A	• No anticoagulation or antiplatelet agents indicated
• **Aortic valve repair**	N/A	N/A	• Aspirin 81 mg daily
Stroke: **Secondary Prevention**			
• **Most patients with non-cardioembolic stroke or TIA (i.e. atherothrombotic, lacunar, or cryptogenic)**	N/A	N/A	• Anti-platelet therapy, either aspirin, aspirin/extended-release dipyridamole Aggrenox), or clopidogrel (Plavix), recommended over anticoagulation
• **Non-cardioembolic stroke or TIA with well documented prothrombotic disorders**	2.0-3.0	2.5	• Oral anticoagulation recommended over anti-platelet agents

• **Atrial fibrillation with recent stroke or TIA**	2.0-3.0	2.5	• Lifetime, unless all anticoagulation contraindicated; then use anti-platelet agent. For strokes associated with AF, DOACs or warfarin can be considered for prevention • In AF with acute ischemic stroke: early anticoagulation (<48 hours) using heparinoids or warfarin should not be used. • Oral anticoagulation should be started within 2 weeks of acute ischemic stroke, but optimal timing within this period is not known. AF with high ischemic stroke risk: use DOAC after acute spontaneous ICH (subdural, subarachnoid, and intracerebral hemorrhages) after careful consideration of risks and benefits of anticoagulation. Note: initiate beyond acute phase (>48 hours) and for at least 4 weeks. (CHEST-2018)
• **Cardioembolic stroke**	2.0-3.0	2.5	• Lifetime, unless anticoagulation contraindicated; then anti-platelet agent
• **Stroke associated with aortic atherosclerotic lesions**	N/A	N/A	• Anti-platelet agents recommended over no therapy
• **Stroke associated with mobile aortic thrombi**	2.0-3.0 if anticoagulated	2.5	• Aspirin 81 mg daily or anticoagulation with warfarin
• **Cryptogenic stroke associated with mobile aortic arch thrombi**	2.0-3.0	2.5	• Either oral anticoagulation or anti-platelet agents
• **Cryptogenic stroke and PFO or atrial septal aneurysm**	N/A	N/A	• Aspirin 75-325 mg recommended; use anticoagulation if another indication, such as DVT, AF, or hypercoagulable state, exists.
• **Recurrent cryptogenic stroke and PFO or atrial septal aneurysm**	2.0-3.0	2.5	• If recurrent stroke on aspirin, warfarin and consideration of closure of PFO suggested.
• **Cryptogenic stroke and PFO or atrial septal aneurysm with associated DVT**	2.0-3.0 (3 months)	2.5 (3 months)	• Warfarin for 3 months and consideration of device closure recommended
• **Mitral valve strands or prolapse with history of TIA or stroke**	N/A	N/A	• Anti-platelet therapy
• **MVP with AF, documented systemic embolism, or recurrent TIAs despite aspirin therapy**	2.0-3.0 If warfarin	2.5 If warfarin	• Lifetime DOAC or warfarin
Anticoagulation during pregnancy – DOACs are never used			
• **DVT/PE during pregnancy or women who become pregnant while on anticoagulation for treatment of DVT/PE**	N/A	N/A	• LMWH; warfarin suggested until pregnancy documented, though may be changed to LMWH in anticipation of planned pregnancy
• **Patients on long-term warfarin, during pregnancy**	N/A	N/A	• At week 6: Discontinue warfarin and replace with LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL), especially in patients with a required warfarin dose >5 mg/day.

			• At week 12: Discontinue LMWH and replace with warfarin (consider maintenance of LMWH as an alternative). • At week 36: Discontinue warfarin and replace with adjusted dose LMWH (with dose adjustment according to weight and target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL) until 24 hours before delivery or cesarean section. (CHEST-2018)
• **Patients with mechanical heart valves**			• Option 1: adjusted dose LMWH during pregnancy to achieve manufacturer's peak anti-Xa LMWH 4 hours after injection • Option 2: Adjusted dose UFH in doses to keep aPTT at least 2x control • Option 3: UFH or LMWH until 13th week, with substitution of warfarin until close to delivery, then UFH or LMWH as above
Anticoagulation for thrombophilias during pregnancy (DOACs never used)			
• **Homozygous Factor V Leiden or prothrombin 20210A mutation with FH VTE but no personal history of DVT/PE**			• LMWH at prophylactic or intermediate-dose LMWH during pregnancy and LMWH at same dose or warfarin at INR 2.0-3.0 for 6 weeks post-partum
• **All other thrombophilias with FH VTE but no personal history of DVT/PE**			• Clinical vigilance during pregnancy, and post-partum prophylaxis with intermediate dose LMWH for 6 weeks or (if not protein C or protein S deficient) warfarin at INR 2.0-3.0 for 6 weeks post-partum
• **Homozygous Factor V Leiden or prothrombin 20210A mutation with no FH VTE and no personal history of DVT/PE**			• Clinical vigilance during pregnancy, and post-partum prophylaxis with intermediate dose LMWH for 6 weeks or warfarin at INR 2.0-3.0 for 6 weeks post-partum
• **All other thrombophilias with no FH VTE and no personal history of DVT/PE**			• Clinical vigilance during pregnancy and post-partum; prophylaxis not recommended
Post-partum anticoagulation			
• **Post-partum after thrombotic event**	2.0-3.0	2.5	• At least 6 weeks after delivery (initially overlapped with UFH or LMWH/Fondaparinux until INR at least 2.0 on 2 consecutive days), for a total of 3 months of anticoagulation
• **Pregnant women with thrombophilia (other than antithrombin deficiency) and no prior VTE**	2.0-3.0	2.5	• After delivery, use warfarin until risk related to pregnancy resolved, generally considered 6 weeks; warfarin (as well as aspirin and LMWH) considered safe for nursing mother; avoid fondaparinux and all DOACs.
Effects of anticoagulation on nursing (Note: DOACs NOT recommended)			

• **Warfarin**			• There is consensus that the effects of warfarin during breastfeeding provide little risk to the infant; when indicated, anticoagulation should continue, and nursing is permitted.[23]
• **Enoxaparin (Lovenox and generics)**			• Due to large molecular weight of 2000 to 8000 Daltons, enoxaparin would not be expected to be excreted into breast milk. No special precautions are required.[24]
Pulmonary hypertension[25]			
• **Idiopathic pulmonary hypertension (confirmed by right heart catheterization)**	1.5-2.5	2.0	• Anticoagulation with warfarin is part of core treatment due to increase in survival; duration = lifetime. When not feasible, off-label use of DOACs may be considered in rare circumstances; note that no currently available studies have evaluated this use in patients with IPH.
• **Pulmonary hypertension occurring in association with other underlying conditions (scleroderma, congenital heart disease, iatrogenic due to diet-pills, chronic lung disease, severe left heart failure)**	1.5-2.5	2.0	• Anticoagulation should be considered per expert opinion, though benefit considered small with weak supportive evidence, and some of these patients have increased risk of GI bleeding. Patients receiving IV prostanoids are at additional risk due to potential for catheter-associated thrombosis, and should be anticoagulated in absence of contraindications.
• **Pulmonary hypertension due to thromboembolic disease**	2.0-3.0	2.5	• Anticoagulation is generally required for underlying condition, and presence of pulmonary hypertension further increases this indication.
• **Indications for patients with high risk for bleeding**			
• **All indications that usually indicate target range of 2.0-3.0, including patients considered high risk for bleeding and requiring management in lower end of therapeutic range**	2.0-2.5	2.25	• This range is not part of any guideline, but may facilitate management of patients deemed at especially high risk of bleeding with elevated INR values yet permit treatment within guideline ranges.
• **Peripheral vascular disease**			
	2.0-3.0	2.5	• ACC/AHA 2016 guideline on PAD recommends antiplatelet agents for treatment of peripheral arterial disease; dual antiplatelet therapy considered reasonable after lower extremity revascularization. These guidelines state: “The

[23] See Lactmed: Warfarin
[24] See Lactmed: Enoxaparin
[25] Badesch, David B et al. Medical Therapy for Pulmonary Arterial Hypertension: Updated ACCP Evidence-Based Clinical Practice Guidelines; CHEST; June 2007; 131(6):1917-1928. doi:10.1378/chest.06-2674

			usefulness of anticoagulation to improve patency after lower extremity autogenous vein or prosthetic bypass is uncertain" and "Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD."[26] However, it remains common practice in certain situations for vascular surgeons to prescribe long-term warfarin for these patients, often after procedures requiring heparin. In these circumstances, when warfarin has been prescribed by the vascular surgeon, AMS will manage the anticoagulation after patient is review by consultant.

[26] 2016 AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease

Prosthetic Valve types and rules:

- Mechanical valves: 3 main categories:
  1. Caged-ball valves: Starr-Edwards (no longer used)
  2. Disc valves: Bjork-Shiley; Medtronic Hall; Monostrut; Omniscience and Omnicarbon; Ultracor
  3. Bileaflet valves: St Jude Medical; Carbomedics; Edwards Tekna; Sorin Biocarbon; ATS Open Pivot; MCRI On-X; Edwards Mira
- All mechanical valves in the mitral position have target INR 3.0, range 2.5-3.5.
- Mechanical valves in aortic position vary depending on thrombogenicity:
  1. High risk valves include caged-ball and some tilting disc valves, including Bjork-Shiley, Monostrut, Omnicience/Omnicarbon, and Ultracor; they have INR target 3.0, range of 2.5-3.5. High-risk aortic valves are no longer implanted; anticoagulation guidelines are based on past recommendations and have not been updated in CHEST-9. All mechanical mitral valves are considered high-risk. If patient has high-risk aortic valve or any mechanical mitral valve, consider addition of aspirin if patient has low risk of GI bleeding.
  2. Lower risk valves include bileaflet and tilting disc Medtronic hall (if no other risk factors and normal LA size); they have INR target of 2.5, range 2.0-3.0.
  3. For 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR, consider bridging anticoagulation therapy during the time interval when the INR is subtherapeutic preoperatively on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures. Note that studies of patients receiving bridging in these situations had a higher risk of bleeding without reduction of thromboembolic events.[27] These considerations require physician consult.
- Biologic Valves (see above for anticoagulation rules):
  1. Porcine, including:
     - Stented porcine valves (sewn onto a stent): Hancock; Carpentier-Edwards (Supra-annular for aortic and mitral positions; Duraflex for mitral position); Biocor; Intact; Mosaic
     - Unstented porcine valves: Toronto SPV; Medtronic Freestyle; Prima Plus; Cryolife O'Brien; Biocor
  2. Bovine pericardial
  3. Homograft

[27] Anticoagulation for valvular heart disease - ACC/AHA-2017 focused update; page 29

Duration of Anticoagulation after DVT/PE:

Relevant factors include the presence of proximal DVT and/or PE (vs. isolated distal DVT), the number of events, provocation of events, persistence of VTE risk factor, the presence of active cancer, and the patient's bleeding risk (see below). Treatment (initial and long-term) can be with warfarin or DOACs unless active cancer or cancer treatment. Differences in anticoagulant risks should be considered based on patient characteristics. Refer to Appendix 10: apixaban (Eliquis), dabigatran (Pradaxa), edoxaban (Savaysa), and rivaroxaban (Xarelto) and Appendix 11: Considerations for Anticoagulant Selection in Atrial Fibrillation and VTE Treatment. Note: we are using HAS-BLED to determine bleeding risks.

- Patients with provoked VTE generally benefit from 3 months of anticoagulation over treatment for a shorter period, treatment for longer time-limited periods (e.g., 6, 12, 24 months), or extended therapy (no scheduled stop date).
- Patients with unprovoked VTE generally benefit from at least 3 months of anticoagulation. For those with a proximal DVT or PE at low-to-moderate bleeding risk, extended anticoagulant therapy (no scheduled stop date) should be considered. For those with a proximal DVT or PE at high bleeding risk, 3 months of anticoagulant therapy should generally be considered, with the possible exception of those who have significant thrombophilia. Patients at high bleeding risk with significant thrombophilia may also benefit from extended treatment when risks of clotting outweigh the risks of bleeding, and/or bleeding can be prevented or easily controlled.

Recommendations and Suggestions for Extended Anticoagulation after DVT/PE[28]			
	Low Bleeding Risk	**Moderate Bleeding Risk**	**High Bleeding Risk**
PE or proximal DVT provoked by surgery	**3 months therapy recommended**	**3 months therapy recommended**	**3 months therapy recommended**
PE or proximal DVT provoked by transient non-surgical risk factor	**3 months therapy recommended**	**3 months therapy recommended**	**3 months therapy recommended**
1st distal DVT provoked by surgery or by a nonsurgical transient risk factor (in whom a decision has been made to anticoagulate)	**3 months suggested**	**3 months suggested**	**3 months suggested**
1st unprovoked PE or proximal DVT	**Extended therapy suggested**	**Extended therapy suggested**	**3 months therapy recommended**
1st unprovoked distal DVT	**3 months therapy recommended**	**3 months therapy recommended**	**3 months therapy recommended**
Recurrent unprovoked VTE	**Extended therapy recommended**	**Extended therapy suggested**	**3 months therapy suggested**
PE or DVT in the presence of active cancer	**Extended therapy recommended***	**Extended therapy recommended***	**Extended therapy suggested***
Known significant thrombophilia in setting of unprovoked VTE**	**Extended therapy recommended**	**Extended therapy recommended**	**Extended therapy can be considered*****

- * *LMWH or DOAC suggested over warfarin*
- ** Presence of thrombophilia should rarely effect determination of duration of treatment, with the possible exception of those at higher bleeding risk. It is the provoked vs unprovoked nature of a VTE that should generally guide treatment decisions. Patients with unprovoked VTE without significant thrombophilia still remain at high risk for recurrence.
- *** *Decision depends on relative risks of bleeding and clotting; must be individualized for patient.*

[28] Adapted from: Kearon, Clive et al; Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. CHEST. February 2016, Vol 149, No. 2

Appendix 2: GUIDELINE FOR WARFARIN DOSE ADJUSTMENT AND MONITORING IN NEW STARTS

Starting Doses and Adjustments

Clinical Status: Initial dosing should be based solely on the patient's clinical status and history**, rather than depending on pharmacogenetic testing.**[29] **Most patients should have an INR target range of 2.0-3.0. Certain very high-risk conditions may require a target range of 2.5-3.5. There is higher bleeding risk, but no decrease in clotting, with higher INR ranges.**

1. **Uncomplicated patients:** Uncomplicated patients include anyone under age 75 who does not have any of the high-risk characteristics below.
2. **Complicated patients:** A patient is considered complicated if s/he has any of the following:
    a. Age 75 years or older,
    b. Frail health with multisystem disease,
    c. Medications which increase the potency of warfarin,
    d. History of therapeutic INR's in the past on low warfarin dosing, or
    e. Known liver disease.
    f. Poor nutrition
    g. Baseline INR elevation above 1.2

Dosing Regimens:

Traditional AMS Approach: 5 mg daily for 3 days, followed by INR-based management

1. **Start therapy at 5 mg (2 tabs of 2.5 mg) daily for first 3 days.**
2. **Check INR on day 4 and adjust dose as follows:**
   - If INR 1.0-1.3, increase to 7.5 mg qd.
   - If INR 1.4 -1.9, keep at 5 mg qd.
   - If INR 2.0-2.9, decrease to 2.5 mg qd.
   - If INR 3.0-3.4, decrease to 1.25 mg qd.
   - If INR 3.5+, hold dose and decrease to 1.25 mg qd.
3. **Repeat INR after 2 days at new dose and adjust dose as follows:**
   - If INR was >3.0 and is now in desired range, maintain same dose unless there has been rapid fall in INR; in this case, may need to increase dose modestly and repeat INR in 2-4 days. If above or below desired range, adjust per maintenance protocols.
   - If INR was below 2.0 and remains below 2.0 but is increasing, continue dose and repeat INR in 2-4 days.

[29] Pharmacogenetic testing for the gene encoding vitamin K epoxide reductase complex (VKORC1) may identify patients more sensitive to warfarin and thus likely to require lower warfarin starting and maintenance doses. However, various analyses have not shown this testing to be cost-effective, and in most situations requirements for dose modifications would already be apparent based on INR monitoring by the time pharmacogenetic results were available. Since patients highly sensitive to warfarin may have lower time in therapeutic range (TTR), use of this testing to identify patients that might have more favorable outcomes on the DOACs has been considered. However, other factors, including efficacy, safety, and cost, are likely to provide more important determinants of this decision. The CHEST-2012 guidelines recommend against routine pharmacogenetic testing.

- If INR was below 2.0 and is now in desired range, either continue dose and repeat INR in 2 days OR decrease dose modestly and repeat in 2-4 days depending on rate of rise of INR.
- If INR was below 2.0 and is now above desired range, hold dose until back in desired range, then adjust dose per maintenance protocols.
- If INR was 2.0-2.9 and is now in desired range, maintain same dose unless there has been rapid rise in INR; in this case, may need to decrease dose modestly and repeat INR in 2-4 days. If above or below desired range, adjust per maintenance protocols.
- If INR was >3.0 and is now in desired range, maintain same dose unless there has been rapid fall in INR; in this case, may need to increase dose modestly and repeat INR in 2-4 days. If above or below desired range, adjust per maintenance protocols.

CHEST-9 Loading Regimen: CHEST-9 suggests a loading dose of 10 mg daily for first two days, based on studies indicating a 1.0-1.3 day earlier time to reach therapeutic range without increase in complications. This option provides the benefit of saving approximately one day of LMWH injections, though is without change in outcome. The approach may add some complexity, since the preferred pill start-up size remains 2.5 mg to facilitate later changes. However, it does modestly decrease the potential duration of LMWH injections and time to reach therapeutic range in many patients.

1. **Start therapy at 10 mg (we recommend 4 tabs of 2.5 mg dose) for first two days.**
2. **Adjust warfarin according to the following nomogram[30]:**

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

[30] From Kovacs, M; Rodger, M; Anderson, D; Morrow, B; Kells, G; Kovacs, J; Boyle, E; and Wells, P; Comparison of 10-mg and 5-mg Warfarin Initiation Nomograms Together with Low-Molecular-Weight Heparin for Outpatient Treatment of Acute Venous Thromboembolism; Ann Intern Med. 2003;138:714-719.

Complicated Patients: (Age 75+, frail with multisystem disease, on drugs that increase potency of warfarin, have had prior at-goal treatment with low doses, have known liver disease, have poor nutrition, or have baseline INR elevations above 1.2)

1. **2.5 mg (1 tab 2.5 mg) per day for 2 days**
2. **INR on day 3 and adjust dose as follows:**

- If INR 1.0-1.3, increase to 3.75 mg qd.
- If INR 1.4-1.9, keep at 2.5 qd.
- If INR 2.0-2.9, decrease to 1.25 mg qd.
- If INR 3.0-3.4, decrease to 1.0 mg qd (order 1 mg tabs).
- If INR 3.5+, hold dose and decrease to 1.0 mg qd (order 1 mg tabs).

3. **Repeat INR after 2 days at new dose and adjust dose as follows:**

- If INR was below 2.0 and remains below 2.0 but is increasing, continue dose and repeat INR in 2-4 days.
- If INR was below 2.0 and is now in desired range, either continue dose and repeat INR in 2 days or decrease dose modestly and repeat in 2-4 days, depending on rate of rise of INR.
- If INR was below 2.0 and is now above desired range, hold dose until back in desired range, then adjust dose per maintenance protocols.
- If INR was 2.0-2.9 and is now in desired range, maintain same dose unless there has been rapid rise in INR; in this case, may need to decrease dose modestly and repeat INR in 2-4 days. If above or below desired range, adjust per maintenance protocols.
- If INR was >3.0 and is now in desired range, maintain same dose unless there has been rapid fall in INR; in this case, may need to increase dose modestly and repeat INR in 2-4 days. If above or below desired range, adjust per maintenance protocols.

Criteria for discontinuation of LMWH/Fondaparinux with newly diagnosed DVT/PE

1. If INR has been therapeutic for two consecutive values after 5 days of treatment with LMWH/Fondaparinux overlapping with Warfarin, stop LMWH/Fondaparinux.
2. If INR is above target range after 4 overlapping days of LMWH/Fondaparinux and warfarin, stop LMWH/Fondaparinux.
3. If INR is above target range after fewer than 4 days of LMWH/Fondaparinux and warfarin, warfarin should be held or decreased until INR falls to therapeutic range. Generally, in these circumstances, LMWH/Fondaparinux will be continued for a total of 4 days unless there is high risk of bleeding (including recent procedure that may predispose to bleeding) or evidence of bleeding. When decision unclear, request assistance from a consultant.
4. If INR has rapidly increased well into target range after 4-5 days of overlapping days of LMWH/Fondaparinux and warfarin, it may be appropriate to discontinue LMWH/Fondaparinux prior to obtaining the second therapeutic range INR. When decision unclear, request assistance from a consultant.

INR Monitoring During Titration To Goal

1. INRs are monitored daily or every other day until the INR $\geq$ 2.0 or as indicated by the referring physician.
2. When the INR and dose of warfarin remain stable and therapeutic for 2 testing days, the INR will be checked every 3-5 days.

3. When the INR and dose of warfarin remain stable and therapeutic for one week, the INR will be checked weekly.
4. When the INR and dose of warfarin remain stable and therapeutic for three weeks, the INR will be checked in two weeks.
5. If the INR remains stable and therapeutic after these two weeks, the INR will be checked in one month.
6. If the INR remains stable and therapeutic on the same warfarin regime for 3 consecutive month, the INR may be checked in 8 weeks.

General Principles: Achieve Day-to-Day stability and steady state as quickly as possible:

1. Only use one strength tablet
2. Always start with 2.5 mg tablets unless patient has previously been treated with either very low doses (e.g. 1 mg daily) or very high doses (e, g.10+ mg daily). The 2.5 mg tablet permits frequent small dose changes by splitting the tablets. If patient has been started on a different strength, request a new prescription for 2.5 mg tablets from referring or current attending physician at the earliest convenient time.
3. Aim for same daily doses. Recalculate alternating doses as soon as possible to achieve same daily dose. If same daily dose is not possible, use 4/3-day alternating schedule, or rarely a 5/2-day. 6/1 schedules should not be used under any circumstances, regardless of previous dosing plans for patients newly enrolled in AMS.
4. If on alternating schedule, assign the day for each dose; do not simply advise “alternate days.”
5. If on alternating schedule, do not use doses that differ by >50% (e.g. 3.75 mg/5.0 mg preferred, 2.5 mg/5.0 mg reasonable; 2.5 mg/7.5 mg not acceptable and should be recalculated).

Appendix 3: GUIDELINES FOR MONITORING PATIENTS TAKING MAINTENANCE DOSES OF ANTICOAGULANTS

1- General Principles of Warfarin Dose Adjustment – When to Adjust Dose:

Stable patient in target range: a patient who has had an INR stable in target range for at least 2 months and presents with another INR that is in range, with no clear trend toward out of range values.

- The dose remains the same.
- Recheck INR in 4 weeks.
- With appropriate counseling, consistently compliant and stable patients may extend testing interval up to 8 weeks before INR check, as long as there are no anticipated medical or surgical interventions that may affect the INR, and as long as any such interventions or medical events do not occur. Patients must be cautioned to notify AMS of any new medical interventions or medication changes. All extended management intervals require a person-to-person conversation, and cannot be done in any circumstances by letter, e-mail, or messages left on phone recording devices.

Stable patient within 0.5 of target range: a patient who has had an INR at goal on a set regimen for at least 2 months and now presents with an INR that is out of range, but within 0.5.

- For patients with target range of 2.0-3, values include 1.5-1.9 and 3.1-3.5; for patients with target range of 2.5-3.5, values include 2.0-2.4 and 3.6-4.0.
- Assess reasons for high or low INR.
- If INR low, may advise make-up dose for one day; if INR high, may advise holding dose for one day; these decisions depend on clinical circumstances.
- If no persistent reason is present, maintenance dose remains the same.
- Recheck INR in 2 weeks.

Previously "active management" patient, now in target range: a patient with prior INR out of range now presents with an INR in target range.

- Dose remains the same.
- Recheck INR in 2 weeks.

"Active management" patient or patient >0.5 out of target range:

- Use the tables below to adjust warfarin dosing in any of the following situations:
  - Patient has an INR more than 0.5 above or below the target range.
  - Patient has an INR out of range with a change in medication or other change in circumstances expected to persist.
  - Patient has a 2nd INR in a row out of range.
- Recheck INR no later than 1 week after low reading or high reading. If markedly out of range, repeat test as indicated by the circumstances.

Patients at high thrombotic risk seriously below target range, especially when related to missed doses:

- When target range is 2.0-3.0 and INR is below 1.5, or target range is 2.5-3.5 and INR is below 2.0, strongly consider a one-time make-up dose of up to three times the usual daily dose. Remember, a single "three-time" dose has the same effect as giving a "two-times dose" two days in a row, but achieves the desired effect a day earlier with no additional risk to the patient. Goal in either case is to achieve an INR in the middle of the target range, not just get into the target range. When INR is only slightly below the target range (e.g. 1.5-1.9 for target range of 2.0-3.0 or 2.0-2.4 for target range of 2.5-3.5, would use a single make-up dose up to two times the usual daily dose.
- Then make an appropriate adjustment in regular dosing if indicated. If low INR was entirely related to missed doses, changing the recommended maintenance plan may not be required.
- In all of these situations, a repeat INR within a week is mandatory.

2- Assessment Prior to Dose Change

Aside from the actual INR value, the most important factors determining the need for a dose change include:

1. Medication compliance
2. Changes in medications, diet, or alcohol consumption
3. Changes in clinical status
4. Most recent INR results – was this an isolated aberrant value or part of a trend.
5. Risk of bleeding or clotting with value out of range
6. Recent or planned procedures that may increase risk of bleeding or clotting.

3- Things to consider when INR is low (see Appendix 6):

1. Is patient taking the correct dose? Ask how many tablets and the exact mg and color of the tablet he/she is taking. Look for warfarin prescription in medication history.
2. Has patient missed any doses? If so, how many days and how long ago?
3. Has patient started, stopped, or changed any other medications (including herbals and over the counter medication including acetaminophen (Tylenol)? Look in medication history.
   - Inducers lower INR levels (speed up the metabolism of warfarin). **Did patient START an inducer, such as phenytoin, phenobarbital, rifampin, or carbamazepine?**
   - Inhibitors raise INR levels (slow down the metabolism of warfarin). **Did patient STOP or decrease the dose of acetaminophen, amoxicillin, amiodarone, Quinolones (ciprofloxacin, Levofloxacin), cimetidine, fluconazole, clarithromycin, erythromycin, metronidazole, or sulfamethoxazole/trimethoprim?**
4. Has patient increased vitamin K in diet (i.e. more dark, green leafy vegetables)?
5. Has patient changed intake of alcohol?
6. Has patient's medical condition changed? Review record for changes in CHF status and thyroid function, and improvement in liver function, or resolution of recent clinical condition that previously increased INR, such as vomiting and/or diarrhea.
7. What is the patient's thromboembolic risk?
   - Is patient being treated for active DVT? If so, you may need to bridge with LMWH/Fondaparinux.
   - Does patient have recurrent DVT or hypercoagulable state? If so, you may need to bridge with LMWH/Fondaparinux.
   - Does patient have high-risk atrial fibrillation? If so, you may need to bridge with LMWH/Fondaparinux.
   - Does patient have INR target 3.0 (goal 2.5-3.5). If so, you probably will need to bridge with LMWH/Fondaparinux if INR is very low.
   - Is subtherapeutic duration already prolonged or expected to be prolonged? If so, you may need to bridge with LMWH/Fondaparinux.

4- Things to consider when INR is high (see Appendix 5):

1. Is patient taking the correct dose? Ask how many tablets and the exact mg and color of the tablet he/she is taking. Has patient started, stopped, or changed any other medications (including herbals and over the counter medications such as acetaminophen (Tylenol))? Look for warfarin prescription in medication history.
2. Has patient taken any extra doses? If so, how many days and how long ago?
3. Has patient started, stopped, or changed any other medications (including herbals)? Look in medication history.
   - Inducers will lower INR levels (speed up the metabolism of warfarin). **Did patient STOP an inducer, such as phenytoin, phenobarbital, rifampin, or carbamazepine?**
   - Inhibitors will raise INR levels (slow down the metabolism of warfarin). **Did patient START an inhibitor, such as amiodarone, ciprofloxacin, cimetidine, fluconazole, clarithromycin, erythromycin, metronidazole, or sulfamethoxazole/trimethoprim?**
4. Has patient decreased vitamin K in diet (i.e. less dark, green leafy vegetables)?
5. Has patient changed intake of alcohol?
6. Has patient's medical condition changed? Review record for changes in CHF status, thyroid function, and liver function. Inquire about vomiting and diarrhea.
7. Consider lab error (as last resort) if INR is high for no apparent reason, or there is marked difference between the fingerstick and venous INR values. If venous INR, ask patient if there were any problems with the blood draw. If tube was not fully filled, then the anticoagulant in the tube may be diluting the blood and contributing to high INR.
8. What is the patient's bleeding risk?
   - What is the patient's bleeding risk score?
   - Is the patient currently experiencing any bleeding (gingival bleeding, epistaxis, ecchymoses, hematuria, melena, blood per rectum, etc.)?
   - Has the patient had any bleeding in the past, especially in the last 2-3 weeks?
   - Has the patient had a procedure or injury that would increase his/her risk of bleeding?
   - Is a procedure planned in the upcoming days?
9. Is patient taking any medication that may interfere with clotting or otherwise increase bleeding risk?
   - Concurrent use of antiplatelet agents (aspirin, clopidogrel (Plavix), aspirin/dipyridamole (Aggrenox) and all virtually all NSAIDS will increase bleeding by interfering with platelet aggregation or adhesiveness. A decrease in platelet function has an additive effect to the risk of bleeding when INR is high.
   - The prostaglandin-blocking effects of NSAIDS and aspirin may cause direct injury to the gastric lining; NSAID-induced ulcers and gastritis may bleed, and the bleeding may be promoted by both the antiplatelet effects of these medications and the patient's elevated INR.
   - In general, one can view the bleeding risk score as increasing at least one bleeding risk point in the presence of aspirin, Plavix, or NSAID use. Though NSAIDS may have more direct effect on the gastric mucosa, their antiplatelet effect generally resolves within a couple days.

5- Guidelines to Regain Specific INR Ranges when intervention is required (including previously unstable patient, new drugs, newly unstable patient, and/or INR >0.5 above or below therapeutic range):

Therapeutic INR Range of 2.0-3.0

INR <2.0 ↓	**INR 3.1-3.7[a]** ↓	**INR 3.8-4.4[b]** ↓	**INR 4.5-4.9[b]** ↓	**INR 5.0-5.9[b]** ↓
Increase weekly dose by 10%-20% ↓	Decrease weekly dose by 10%-20% ↓	Hold 1 to 2 doses then decrease weekly dose by 15%-20% ↓	Hold 1 to 2 doses then decrease weekly dose by 20%-25% ↓	Hold 2 to 3 doses then decrease weekly dose by approximately 20%-25% ↓
Monitor INR within 2 weeks of changed dose		Monitor INR within 1 week of changed dose		Monitor INR every 3 to 4 days for at least 1 week

[a] Note that the above box refers to unstable patients in the 3.1-3.5 range and all patients in the 3.6-3.7 range. If the INR is 3.1-3.5 and had previously been therapeutic and stable on the present dose, and cause for high INR (e.g. additional warfarin dose, less Vitamin K in diet, change in alcohol intake, or temporary interacting medication) has resolved, or if cause is unknown, consider decreased dose for one to two days, and then resume prior dose with repeat INR in 2 weeks. If the INR is 3.6-3.7, make appropriate adjustment based on similar parameters and repeat INR in 1 week,

[b] INR values 4.0 and above done by fingerstick at Atrius Health will be confirmed by a venous sample. Venous results may vary up to 2.0 units in the higher ranges of elevation. Therefore, in some cases, a provisional plan may require later revision after receipt of the final result.

Therapeutic INR Range of 2.5-3.5

INR <2.5 ↓	**INR 3.6-4.0[c]** ↓	**INR 4.1-4.5[d]** ↓	**INR 4.6-4.9[d]** ↓	**INR 5.0-5.9[d]** ↓
Increase weekly dose by 10%-20% ↓	Decrease weekly dose by 10%-20% ↓	Hold 0 to 1 dose then decrease weekly dose by 15%-20% ↓	Hold 0 to 1 doses then decrease weekly dose by ~20% ↓	Hold 1 to 2 doses then decrease weekly dose by ~20% ↓
Monitor INR within 2 weeks of changed dose		Monitor INR within one week of changed dose		Monitor INR every 3 to 4 days for at least 1 week

[c] If the INR is 3.6-4.0 and had previously been therapeutic and stable on the present dose, and cause for high INR has resolved (e.g. additional warfarin dose, less Vitamin K in diet, change in alcohol intake, or temporary interacting medication), or if the cause is unknown, consider decreased dose for one to two days, and then resume prior dose with repeat INR in 2 weeks. For other patients, i.e. not identified as previously therapeutic and stable, adjust dose as recommended in the above box.

[d] INR values 4.0 and above done by fingerstick at Atrius Health will be confirmed by a venous sample. Venous results may vary up to 2.0 units in the higher ranges of elevation. Therefore, in some cases, a provisional plan may require later revision after receipt of the final result.

Therapeutic INR Range of 1.5-2.0[31, g]

INR <1.3 ↓	**INR 1.3-1.4** ↓	**INR 2.1-3.0** ↓	**INR 3.1-4.0** ↓	**INR 4.1-5.9** ↓
Increase current dose by 15%-20% ↓	Increase current dose by 10%-15% ↓	Decrease current dose by 10%-15% ↓	Hold 1 to 2 doses then decrease weekly dose by ~20% ↓	Hold 2 to 3 doses then decrease weekly dose by ~20% ↓
Monitor INR within one week	Monitor INR within 2 weeks		Monitor INR within one week	Monitor INR every 3 to 4 days for at least 1 week

[g] Apply above monitoring considerations; note that this range has been found to be less effective for extended prevention of DVT than 2.0-3.0, without conferring a decrease in bleeding risk.[32]

Therapeutic INR Range of 1.8-2.3 [h]

INR <1.5	**INR 1.6-1.7**	**INR 2.4-3.3**	**INR 3.4-4.3**	**INR 4.4-5.9**
Increase current dose by 15% ↓	Increase current dose by 10% ↓	Decrease current dose by 10%-15% ↓	Hold 1 to 2 doses then decrease weekly dose by ~20% ↓	Hold 2 to 3 doses then decrease weekly dose by ~20% ↓
Monitor INRs based on new therapy guideline.				

[h] This target range most commonly applies to patients with recent joint replacement, who have a relatively short-term indication for anticoagulation. Therefore, start-up rather than the above maintenance principles for dosing usually apply.

[31] Ridker, PM, Goldhaber, SZ, et al, "Long-Term, Low-Intensity Warfarin Therapy for Prevention of Recurrent Venous Thromboembolism." New England Journal of Medicine, vol. 348, no. 15, Apr 10, 2003

[32] Kearon, C. "Long-term management of patients after venous thromboembolism." Circulation. 2004 Aug 31; 110(9 Suppl 1):I10-8.

6- INR Monitoring Standards for Patients on Maintenance Therapy

1. Once patients have completed the active management phase of treatment, monitoring should proceed with INRs every 4 weeks.
2. With appropriate counseling, consistently compliant and stable patients may extend testing interval up to 8 weeks before INR check, as long as there are no anticipated medical or surgical interventions that may affect the INR, and as long as any such interventions or medical events do not occur. Patients must be cautioned to notify AMS for any new medical interventions or medication changes. When initiating an extended management interval, AMS Staff will engage in a person-to-person conversation via phone or e-mail.
3. After a dose change, reassess:
   - Patients with non-therapeutic INRs who were *previously unstable* → in one week.
   - Patients with non-therapeutic INRs who were *previously stable* → in two weeks.

7- INR Monitoring Standards for Patients on Concomitant Drug Therapies

Please see Warfarin Drug-Drug Interactions section for specific INR testing guidance surrounding warfarin drug interactions

8- Monitoring protocol for cardioversion of atrial fibrillation/atrial flutter and ablation of atrial flutter:

Prior to procedure:

1. Monitor INR weekly for four weeks before cardioversion and/or ablation. Adjust dose to maintain INR at least 2.0, aiming for target in the high end of the 2.0-3.0 range.
2. If INR falls below 2.0, increase dose of warfarin as indicated, notify the cardiologist, and advise patient that the planned date MAY need to be postponed or have a TEE added (more likely). Repeat INR within one week. Bridging is only required if otherwise indicated by CHA2DS2-VASc criteria or due to other risk factors (e.g. mechanical valves) that would indicate bridging. The key interventions include the management of the INR to goal range and the possible delay in the date of the planned cardioversion and/or ablation. The scheduling will be confirmed by Cardiology.
3. Last INR preceding cardioversion is checked within 3 days of cardioversion, ideally the day before the procedure; result reviewed by AMS manager. AMS manager will notify cardiologist of result.
4. Assuming INR has been at least 2.0 for all weekly tests, at least three consecutive weeks (four weekly values):
   - CV will be performed at INR 2.0-4.2.
   - Cardiologist will make case-by-case decision for INR in range >4.2.

First four weeks after procedure:

1. Monitor INR weekly for four weeks after procedure. Adjust dose to maintain INR at least 2.0, aiming for target in the high end of the 2.0-3.0 range.
2. If INR falls below 2.0, increase dose of warfarin as indicated, start LMWH in treatment dose range, and recheck INR in 1-2 days. Continue LMWH until INR≥2.0. Presume that bridging will occur, but notify cardiologist in case he/she wishes to exempt patient from bridging. Anticipated treatment should not be delayed while awaiting cardiologist's response.

Beyond four weeks after procedure: Return to usual management and bridging guidelines.

9- Monitoring protocol for ablation of atrial fibrillation (pulmonary vein isolation):

Note: this procedure carries a greater and longer risk of thromboembolic events than simple cardioversion of atrial fibrillation or atrial flutter and ablation of atrial flutter. Thus, the post-procedure period of weekly monitoring needs to be extended to 8 weeks. If INR falls below 2.0, the cardiologist needs to be notified, and bridging with LMWH should routinely occur.

Prior to procedure:

1. Monitor INR weekly for four weeks before pulmonary vein isolation. Adjust dose to maintain INR at least 2.0, aiming for target in the high end of the 2.0-3.0 range.
2. If INR falls below 2.0, increase dose of warfarin as indicated and notify the cardiologist scheduled to perform the procedure. Repeat INR within one week. Bridging is only required if otherwise indicated by CHA2DS2-VASc criteria or due to other risk factors (e.g. mechanical valves) that would indicate bridging. The key intervention is the management of the INR to goal range.

First eight weeks after procedure: Note: radiofrequency ablation of atrial fibrillation is a special situation with increased risk of thromboembolism (1-2% over 3 months post ablation, with most events in the first month).

1. Monitor INR weekly for eight weeks after procedure.
2. If INR falls below 2.0, increase dose of warfarin as indicated, start LMWH in treatment dose range, and recheck INR in 1-2 days. Continue LMWH until INR≥2.0. Presume that bridging will occur, but notify the cardiologist who performed the procedure in case he/she wishes to exempt patient. Anticipated treatment should not be delayed while awaiting cardiologist's response.

Beyond eight weeks after procedure, up to 3 months after procedure: contact cardiologist for decision on bridging, which will be individualized based on clinical factors. Page cardiologist if response not received by Staff Message within one hour.

10- INR Monitoring Standards for of Interrogations of AICDs with Defibrillation Threshold Testing[33]

Prior to procedure:

1. Monitor INR weekly for four weeks before Interrogation of AICDs with defibrillation threshold testing. Adjust dose to maintain INR at least 2.0, aiming for target in the high end of the 2.0-3.0 range. Doses are adjusted to maintain INR at least 2.0, aiming for target in high end of 2.0 to 3.0 range.
2. AMS manager reports any INR below 2.0 to cardiologist.
3. Last INR preceding cardioversion is checked within 3 days of AICD Interrogation, ideally the day before the procedure; result reviewed by AMS manager. AMS manager will notify cardiologist of result.
4. Assuming INR has been at least 2.0 for all weekly tests, at least three consecutive weeks (four weekly values):
   - Procedure will be performed at INR 2.0-4.2.
   - Cardiologist will make case-by-case decision for INR in range 4.2-5.0.
   - Procedure will be postponed at INR >5.0 – AMS manager will notify cardiologist to coordinate plan.

First four weeks after procedure:

1. Anticoagulation will continue at least 4 weeks after the procedure, to be discontinued on direction of the cardiologist.

[33] If patient is having a simple interrogation without defibrillation threshold testing (similar to interrogation of pacemaker), there are no anticoagulation requirements.

2. Monitoring during this time will follow usual testing guidelines, with bridging based on the CHA2DS2-VASc or other relevant risk factors when and if required.

11- INR Monitoring Standards for Pacemaker and AICD Placement, and ablations where a change in rhythm may occur

The majority of Electrophysiology (EP) procedures are now being done on uninterrupted warfarin. When warfarin is held, it is typically for 3-5 days at most and rarely requires bridging. If the Cardiology office note is not clear on the recommended plan, please directly verify with the EP physician.

12- INR Monitoring Standards for ablations where no change in rhythm is anticipated

Procedures such as AV nodal ablations in the context of existing atrial fibrillation, where no change in baseline rhythm is anticipated during or after the procedure, can be done on therapeutic warfarin dose. There is no need to rigorously monitor INR, just ensure that the INR is less than 3.5 at the time of the procedure. An INR within 2 days of the procedure, assuming that it is in therapeutic range and below 3.5, would indicate that it is reasonable to proceed.

13- INR Monitoring Standards for routine cardiac catheterizations

For coronary angiography or left heart catheterization (which involves arterial puncture and often goes on to an angioplasty or stent procedure) most are now performed via radial approach with low bleeding risk. A four-day hold of warfarin on all patients (regardless of baseline INR will bring most patients to a range suitable for the procedure. For DOACS, standard hold would apply; for apixaban, edoxaban, and rivaroxaban, last dose taken 2 days before surgery would be a reasonable approach. For dabigatran, last dose should be taken:

- 2 days before surgery for creatinine clearance ≥80 mL/min
- In morning 2 days before surgery for creatinine clearance 50-79 mL/min
- 3 days before surgery for creatinine clearance 30-49 mL/min

The cardiologist performing the procedure will tell the patient when to resume anticoagulation post-procedure, most typically be on the evening of the procedure.

For right heart catheterization (only venous puncture required, typically under ultrasound guidance), it would be reasonable to proceed as long as INR is below 3.0, and to proceed with normal use of DOACs, holding the morning dose on the day of the procedure, resuming after the procedure with the permission of the cardiologist.

In general, for all procedure holds in patients taking warfarin, we advise next INR check a week after resuming anticoagulation.

14- INR Monitoring Standards for placement of the Watchman Device

Anticoagulation is required for this procedure, since atrial thrombus may exist at baseline. To minimize the risk of thrombus at the time of the procedure, weekly INRs are required for the four weeks prior to the procedure. Since all patients have an intraoperative TEE to evaluate for thrombus, a subtherapeutic INR during this period will not cause delay in the procedure or bridging, but should be forwarded to the cardiologist performing the procedure. In addition, weekly INRs should occur for 4 weeks following the procedure, but subtherapeutic results do not require bridging, just rapid management to bring to therapeutic range. Note that patients having this procedure will be taking aspirin in addition to warfarin. After 45-60 days, all patients will have a repeat TEE to ensure the appendage has been totally occluded with no residual leaks. If so, patients can then stop warfarin and remain in aspirin/clopidogrel for 6 months.

15 – MONITORING STANDARDS FOR PATIENTS ON DOACS

DOAC MONITORING

- Anticoagulants as a class are one of the highest risk therapies in regards to adverse events and bleeding events with DOACs in particular may be more costly than with warfarin. [34,35,36,37,38]
- Although DOACs do not require routine monitoring of clotting assays, monitoring renal function and systematic follow up to ensure good adherence, monitor bleeding and clotting risks, confirm appropriate dosing, manage drug-drug interactions, and coordinate periprocedural management is essential to a safe and effective treatment plan.
- DOACs are more expensive than warfarin and cost barriers can contribute to poor DOAC adherence during the first 4 to 6 months of therapy, which has been shown to lead to worse clinical outcomes.[36,39,40]
- Anticoagulation management services have been shown to improve appropriate medication dosing and patient adherence compared to management by a primary physician, with clinical interventions being made in up to 68.1% of patient follow-up visits.[55]
- Upon referral to Atrius Health AMS, DOAC patients are managed using either the "Initial DOAC Management Plan" or the "Active Surveillance Management Plan".

Initial DOAC Management Plan

- Used for patients that have been on DOAC therapy for < 6 months
- The Initial Management Plan is designed to guide anticoagulation managers through systematic assessment of baseline labs, bleeding and clotting risks, drug-drug interactions, medication adherence, and to provide patient education. Frequent follow up occurs on a scheduled basis for the first 6 months of treatment as this is the highest risk period for bleeding events and poor compliance.[41,42]
- After AMS enrollment and initial education of patient at time of referral, telephone follow up calls are made at 1-3 weeks, 3 months, and 6 months
  - VTE Patients (Apixaban, Dabigatran, Edoxaban) – 1 week follow up should occur at the time of DOAC dose adjustment or transition from LMWH to DOAC
  - VTE Patients (Rivaroxaban) – follow up at 3 weeks at time of dose adjustment (instead of at a 1 week)
- If patients are referred to AMS within the 6 month period and DOAC treatment has already been initiated, the Initial Management Plan should be followed beginning at the next scheduled follow up relative to the patient's start of therapy (i.e., if patient taking DOAC for 1 month, next scheduled follow up after initial enrollment would be at 3 month point)

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[41] Hellenbart E, Faulkenberg K, Finks S. Evaluation of bleeding in patients receiving direct oral anticoagulants. Vasc Health Risk Manag. 2017;13:325-342.

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- The **DOAC Monitoring Checklist** created by Thrombosis Canada should be filled out during the Initial Management Plan follow ups and can be used to guide AMS managers through the areas of assessment below.

Areas of Assessment For Each Scheduled Initial Patient Follow Up	
Health Status	• New relevant medical problems, ED visits/hospitalizations? • Embolic events (stroke, TIA, systemic embolism)?

Adherence	• Assess missed doses:
	  ○ "Some people have trouble remembering to take their medications. In the past week, including weekends, how many doses have you missed for one reason or another?"
	  ○ Review refill data if available in Epic via Rx benefits or if patient filling at Atrius pharmacy
	• Issues taking DOAC as directed (e.g., with food (rivaroxaban 15/20mg), storing in original container, not chewing or opening capsule (dabigatran)
	• Re-educate on importance of strict medication schedule
	• Inform about adherence aids if needed (special boxes; smartphone applications)
	• Inquire about any cost issues the patient may have with the medication

Bleeding Risk Assessment	Assess for any signs/symptoms of bleeding: • Nuisance bleeding: preventive measures possible? Motivate patient to diligently continue anticoagulation • Bleeding with impact on quality-of-life: prevention possible? Need for revision of anticoagulation dose or timing? • Change in hemoglobin or new anemia if checked recently Assess for any risk factors for bleeding: • Uncontrolled BP (SBP >160 mmHg or DBP >95) – f/u plan for BP management should be in place with PCP or specialist. • Hypotension with syncope/fall – PCP team or relevant specialist should evaluate for reduction in possible contributing medications and patient should have fall risk assessment • Excessive alcohol intake. • Medication use – NSAIDs, aspirin, etc.: NSAIDS should be taken only when absolutely necessary, and should be cleared with the PCP or anticoagulation manager managing the patient. Aspirin may be used in addition to DOAC in some clinical circumstances, but should never be taken in the absence of a clear clinical indication, such as acute coronary syndrome or presence of a vascular stent.
Lab Monitoring	Serum Creatinine/CrCl Calculation (per Cockcroft-Gault): • If last CrCl >60mL/min: every 12 months • If last CrCl 30-60mL/min: every 6 months • If last CrCl <30mL/min: every 3 months
Other Side Effects	• Carefully assess relation to DOAC: requires decision and motivation of patient when DOAC continued despite side effects. In some situations, temporary cessation or change of drug may be indicated.
Procedures	• Instruct patient to inform AMS of any upcoming procedures or surgeries. • Outline AMS role of providing periprocedural plan in coordination with PCP, interventionist, and other care team members.
Drug Interactions	• Applies to prescription and over-the-counter drugs • Careful interval history: note that even temporary use of interacting drugs expose patients to periods of under-anticoagulation and over-anticoagulation, depending on the type of interacting drug.

	• If NSAIDS are needed or if concomitant antiplatelet therapy is required in addition to DOACs, always consider addition of a PPI.
Final Assessment	Based on above, re-assess: • If chosen DOAC is best anticoagulant for patient • If chosen dose is correct
Education	• Rationale for continued DOAC therapy • Potential for minor, major, or life-threatening bleeding • Dosing instructions, adherence, risks of non-adherence, handling missed doses • Avoiding OTC ASA + NSAIDs except when clinically necessary, and minimizing alcohol use to reduce bleeding risks • Next follow-up call and lab work

Active Surveillance DOAC Management Plan

- Used for patients that have been on a DOAC for > 6 months
- The Active Surveillance Management Plan is designed to follow patients longitudinally using as needed follow up in order to ensure appropriate dosing of DOAC, proper adherence of medication and laboratory monitoring, assess drug-drug interactions, and coordinate periprocedural management of anticoagulation. After the 6 month point, patients have been stabilized on their anticoagulation therapy and are no longer within the high risk initial treatment period.
- Patients will either transition to Active Surveillance after their 6 month Initial Management Plan follow up, or be initiated directly into Active Surveillance if they are referred to AMS after already being on DOAC for > 6 months.
- Creatinine should continue to be drawn at the same intervals used for the Initial Management Plan. Normal lab results will be delivered via letter or MyHealth message indicating that no change in DOAC therapy is needed at this time
- The patient will be assessed at least yearly for appropriateness of continued anticoagulation.

Appropriate Reasons for Telephone Follow-up During Active Surveillance	
Peri-procedural plans	• Includes follow up 2 to 3 weeks prior to procedure to review plan with patient and on POD#1 to ensure anticoagulation therapy was restarted post-operatively
DOAC dose adjustments	• Follow ups should be scheduled within 1 week of any anticipated dose reduction based on age • Patients with borderline renal function or weight should be contacted once dose adjustment threshold has been crossed or if updated lab results or patient provided information is required
Recent hospitalizations or ED visits	• Only required if admission or evaluation is related to bleeding, clotting if changes to DOAC therapy were made
Low Adherence (< 80%)	• Adherence reports will be generated at the beginning of each month and patients with scores < 80% will receive follow up to discuss potential barriers to therapy • Referring physician to be contacted if adherence score does not improve after 3 months
Drug-Drug Interactions	• Follow up required if drug-drug interaction results in change to DOAC dose or requires transition to alternative anticoagulant • Medication lists are assessed on a continuous basis using Best Practice Alerts
Overdue lab testing	• All patients overdue for lab testing will receive reminder calls and physician notification as outlined in Compliance With Lab Monitoring For Anticoagulation Patients section

Appendix 4: GUIDELINE FOR INITIAL OUTPATIENT TREATMENT OF VENOUS THROMBOSIS AND PULMONARY EMBOLUS[43] [44]

Target Population: Patients suitable for outpatient management of VTE under AMS protocols include most hemodynamically stable patients with newly confirmed VTE or suspected pulmonary embolus. Usual protocols may not apply to the following groups and will require AMS consultation before enrollment:

- Pregnant patients (generally are treated with LMWH)
- Morbidly obese patients – see below under Further Considerations re: VTE prophylaxis and treatment (American Society of Hematology VTE Guidelines, with some caveats)[45]

In addition, some other patients may not be suitable for our protocols, and therefore will also require AMS consultation before enrollment:

- Patients on hemodialysis
- Patients with active bleeding

Treatment: initial treatment options include low molecular weight heparin (LMWH) or fondaparinux plus warfarin (warfarin) transitioning to warfarin alone, LMWH long-term, LMWH or fondaparinux plus DOAC (dabigatran or edoxaban) transitioning to DOAC alone, or DOAC alone (apixaban or rivaroxaban). CHEST-2016 suggests DOAC as first choice, though several patient considerations may contribute to the preferred choice.

See table in Appendix 11: Considerations for Anticoagulant Selection in Atrial Fibrillation and VTE Treatment

- **Baseline laboratory evaluation:**
  1. Prothrombin time as measured by International Normalized Ratio (INR)
  2. Serum creatinine – if not known
  3. Complete Blood Count (CBC), primarily to have baseline platelet count, but also to have baseline hemoglobin in event of bleeding
  4. ALT (SGPT)
  5. HCG, if indicated

- **Treatment options**
  1. **LMWH/Fondaparinux options (See Appendix 6):**
     - Enoxaparin sodium (Lovenox) 1 mg/kg subcutaneously (sc) every 12 hours or 1.5 mg/kg (sc) once daily[46]

[43] Adapted from CPAS Policy and Procedures, Kaiser Permanente Clinical Pharmacy Anticoagulation Service

[44] See also: AF and VTE Fact Sheet

[45] DOACs are not generally recommended in patients with BMI>40. LMWH (enoxaparin) can be used up to BMI 48.0 (but would definitely need twice daily dosing) + warfarin until INR ≥2.0 on two consecutive days. When apixaban is used in a patient with a BMI >40 kg/m2 or weight >120 kg, The International Society on Thrombosis and Haemostasis (ISTH) suggests measuring peak and trough levels using an antifactor Xa assay or mass spectrometry. If drug level is below the expected range, ISTH suggests changing to a vitamin K antagonist rather than adjusting the dose of apixaban (ISTH [Martin 2016]). There is some evidence that DOACs can be used in patients who are morbidly obese, as noted in http://www.tandfonline.com/doi/abs/10.3109/07853890.2014.982064?src=recsys&journalCode=iann20

[46] Kearon et al; Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines - 2012; 5.4.2: "*In patients with acute DVT or PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C). Remarks: This recommendation*

- Dalteparin (Fragmin)
  - **Acute pulmonary embolism (non-cancer-related) (off-label use):** SubQ: 120 units/kg twice daily (Meyer 1995) **or** 200 units/kg once daily (Kovacs 2000). **Note:** Start warfarin on the first treatment day and continue dalteparin until INR is ≥2 for at least 24 hours (usually 5 to 7 days) (ACCP [Guyatt 2012]).
  - **DVT (with or without PE; non-cancer-related) treatment (off-label use in US):** SubQ: 200 units/kg once daily (AHA [Jaff 2011]; Feissinger 1996; Wells 2005) or 100 units/kg twice daily (AHA [Jaff 2011]). **Note:** Use of once daily dalteparin dosing regimen is suggested. Start warfarin on the first treatment day and continue dalteparin until INR is ≥2 for at least 24 hours (usually 5 to 7 days) (ACCP [Guyatt 2012]).
  - **Special considerations:** for CrCl <30 mL/min, manufacturer recommends monitoring factor Xa levels; for hepatic insufficiency, use with caution.
- Fondaparinux
  - If patient weighs <50 kg, Fondaparinux 5mg subcutaneously once daily
  - If patient weighs 50-100 kg, Fondaparinux 7.5mg subcutaneously once daily
  - If patient weighs >100 kg, Fondaparinux 10mg subcutaneously once daily

2. **Warfarin:** 2.5 mg tablets per protocol (see Appendix 2: Guideline for Dose Adjustment and Monitoring in New Starts).
   - If <75 years old, advise 5mg (two 2.5mg tablets) each night for 3[47] nights, then check morning INR. For healthy patients with no comorbidities, consider starting at 10mg (four 2.5 mg tablets) for two days and then check morning INR as noted in Appendix 2 above.
   - If 75+ years old, advise 2.5mg (1 tablet) each night for 2[48] nights, then check morning INR.

3. **DOAC (Apixaban, dabigatran, edoxaban, and rivaroxaban) prescriptions:** suggested by CHEST-2016 as preferred option. See decision points above and Appendix 11 for guidance on anticoagulant selection. Also note, all DOACs cost more than warfarin, in most cases to the patient as well as the capitated health care provider. When DOAC chosen as initial management, apixaban (Eliquis) and rivaroxaban (Xarelto) are preferred. Dabigatran (Pradaxa) requires initial treatment with LMWH, so offers no advantage over warfarin, and also has more potential side effects (in particular, GI) and no less complexity of management. Edoxaban (Savaysa), though non-inferior to warfarin for treatment of VTE, shares the increased expense of the other DOACS and requires an initial start of LMWH.

- **Use the following referrals to the Anticoagulation Management Service (see also Referral and Enrollment):**
  1. For referral to Warfarin Anticoagulation Management Service, place REFERRAL TO WARFARIN-ANTICOAG [REF195].
  2. For referral to DOAC Anticoagulation Management Service, place REFERRAL TO DOAC ANTICOAG [REF195A].
  3. Access both referrals by typing "Ref anticoag…" in orders.
  4. Referral must include medication, indication, INR target rage (if on warfarin), and duration of anticoagulation; otherwise, referral is not considered complete.
  5. Referral is considered complete only after AMS manager acknowledges receipt of referral and has made contact with patient.
  6. Referral must be received before 4PM on Monday-Thursday and before 3PM on Friday; otherwise, anticoagulation management of the patient remains the responsibility of the referring physician or his/her coverage until the next business day.

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only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (i.e., the once-daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day." Unfortunately, this recommendation does not apply to enoxaparin, since the maximum approved 24-hour dose is 1.5 mg/kg, not double the dose used for twice-daily dosing (1 mg/kg bid). Enoxaparin in once-daily dosage is only approved for inpatient treatment of DVT/PE, though is often used off-label in outpatient settings for this purpose when twice-daily dosing is impractical or impossible.

[47] If increased sensitivity to warfarin suspected (liver disease, unstable co-morbid conditions, drugs that increase warfarin effect, existing mild elevation of baseline INR, or previous very low warfarin dose), check INR after second dose (day 3); starting dose in these situations will generally be 2.5mg daily (lower if clinically indicated).

[48] If feasible, these patients should be checked on day 3 after 2 doses.

7. AMS managers operate under the delegation of the PCP or PCP surrogate; thus, the clinical management of the patient remains the responsibility of the referring PCP or PCP surrogate at all times.
8. The PCP or PCP surrogate must cosign prescriptions for DOAC, warfarin, LMWH, Fondaparinux and vitamin K, except in the case of prescriptions written by a thrombosis CDTM credentialed clinical pharmacist
9. In warfarin patients requiring consideration of bridge therapy, the AMS manager will make recommendation to PCP or PCP delegate based on guideline and/or consultation with a consultant. PCP or PCP surrogate will make final decision on need for bridge therapy after receiving this recommendation.
10. In situations requiring consideration of Vitamin K to reverse a high INR, assuming patient is clinically stable and not having severe bleeding, the AMS manager will make decision to treat based on guideline and/or consultation with a consultant. After hours and on weekends, the AMS staff will typically make this decision and work with Telecom, or Urgent Care to order the vitamin K if appropriate. When the patient has severe bleeding or is otherwise clinically unstable, the AMS manager (or Urgent Care/Telecom clinician) will direct the patient to the ER and notify the PCP or PCP delegate.
11. The PCP or PCP surrogate will oversee administration and education on the use of LMWH/Fondaparinux, including:
    1. Arrangements for education to allow self-injection or injection by family member.
    2. Arrangements for return to office for injection by appropriate clinical staff (if needed).
    3. Arrangements for VNA services for injection if patient is homebound.
12. AMS managers will write all INR lab orders after baseline pre-treatment labs.

- **After Day One, while patient remains on LMWH/Fondaparinux and Warfarin:**
  - See Appendix 2: Guideline for Dose Adjustment and Monitoring In New Starts.
  - Frequency of patient visits depends on clinical issues; phone contact should include assessment for symptoms of pulmonary embolus (PE), clot extension and bleeding.
  - Goal of initial treatment: at least 5 days of LMWH/Fondaparinux and 2 consecutive INRs in therapeutic range
- Note: although compression stockings may be used for management of symptoms during acute and chronic DVT, they are not indicated solely for prevention of postphlebitic syndrome.

Further Considerations re: VTE prophylaxis and treatment (American Society of Hematology VTE Guidelines, with some caveats)[49]

- Extended-duration outpatient VTE prophylaxis for critically ill or medically ill patients is NOT recommended over just using prophylaxis during the inpatient stay.
- In those at substantially increased risk of VTE (e.g., recent surgery, prior history of VTE, postpartum women, active malignancy, or ≥2 risk factors, including, combinations of the above with hormone replacement therapy, obesity, or pregnancy), graduated compression stockings or prophylactic LMWH for long-distance (>4 hours) travel is suggested. If LMWH or graduated compression stockings are not feasible, aspirin is suggested over no VTE prophylaxis.[50]

[49] American Society of Hematology VTE Guidelines-2018

[50] Although long-distance travel clearly increases the risk of venous thrombosis, the existing evidence of benefits of pharmacologic intervention remains unclear. A rational approach to travelers at high risk of venous thrombosis planning flights at least 4-6 hours includes (1) prudent and risk-free measures such as ambulation at least every two hours, calf muscle and knee/thigh muscle stretching exercises, avoiding dehydration and excessive alcohol consumption and sedative drugs that may impair mobility, (2) use of compression stockings***,*** *and (3) consideration of a single dose of LMWH prior to departure when desired by patient and low bleeding risk exists (adapted from* UpToDate-prevention of venous thromboembolism in adult travelers).

- In obese patients receiving LMWH therapy for treatment of acute VTE, initial LMWH dose selection according to actual body weight rather than dose selection based on a fixed maximum daily dose (i.e., capped dose) is suggested.
- For obese patients or patients with CrCl <30mL/min receiving LMWH therapy for acute VTE treatment, anti-factor Xa concentration monitoring to guide LMWH dose adjustment is NOT suggested.[51]
- For patients requiring inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A4, an alternative anticoagulant (such as warfarin or LMWH) rather than a DOAC is suggested. This recommendation places a high value on avoiding the uncertainty in DOAC anticoagulant response and a low value on avoiding the burden of warfarin or LMWH therapy. Patients strongly adverse to INR monitoring or daily injections are likely to remain on DOACs, whereas avoiding DOACs in favor of warfarin may be favored in the very elderly, those with compromised renal function, and situations where multiple drugs affecting P-gp and/or CYP enzymes are co-prescribed.[52]
- For patients transitioning from DOAC to warfarin, overlapping DOAC and warfarin therapy until the INR is within the therapeutic range is suggested over using LMWH or UFH bridging therapy.
- Measuring the DOAC anticoagulant effect during management of bleeding or prior to scheduled invasive procedures is not recommended.
- For patients on warfarin at low to moderate risk of recurrent VTE, periprocedural bridging is not recommended.
- For patients who survive an episode of major bleeding, resumption of oral anticoagulation therapy within 90 days rather than discontinuation of oral anticoagulation therapy is suggested for patients who require long-term or indefinite therapy, are not at high risk of recurrent bleeding, and are willing to continue therapy.[53]
- For patients taking DOACs with CrCl ≥60mL/min, monitor renal function every 12 months, for patients taking DOACs with CrCl 30-60 mL/min, monitor renal function every 6 months, and for those with CrCl <30mL/min, monitor renal function every 3 months.
- DOACs are a recommended anticoagulant option for patients with acute HIT, subacute HIT (suggested over warfarin in these patients), or remote HIT - see Appendix 13: Heparin-Induced Thrombocytopenia (HIT)

[51] Note also: DOACs are not generally recommended in patients with BMI>40. LMWH (enoxaparin) can be used up to BMI 48.0 (but would definitely need twice daily dosing) + warfarin until INR ≥2.0 on two consecutive days. When apixaban is used in a patient with a BMI >40 kg/m2 or weight >120 kg, the International Society on Thrombosis and Haemostasis (ISTH) suggests measuring peak and trough levels using an antifactor Xa assay or mass spectrometry. If drug level is below the expected range, ISTH suggests changing to a vitamin K antagonist rather than adjusting the dose of apixaban (Martin, K, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. Journal of Thrombosis and Haemostasis; vol 14, issue 6; June 2016;Pages 1308-1313. There is some evidence that DOACs can be used in patients who are morbidly obese (Dimmo, M. et al. Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: A meta-analysis of randomized controlled trials. Annals of Medicine; vol 47, 2015; issue 1; pages 61-68).

[52] Our decision-making on use of DOACs in the presence of interacting drugs follows a more nuanced approach, as noted in AF and VTE Fact Sheet

[53] Resources to inform decision on resumption of anticoagulation after bleeding episodes also includes: the 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants. Journal of American College of Cardiology. December 2017 and the Anticoagulation Toolkit

Appendix 5: GUIDELINES FOR MANAGING PATIENTS WITH HIGH INR VALUES

General Principles:

1. Patients with reports of ***bleeding of unclear significance*** when coupled with elevated INR (at any level) are reported to PCP. The PCP is responsible for making a determination about the need for further evaluation or treatment.
2. Patients ***with significant bleeds*** are reported to the patient's PCP and sent to the emergency room for evaluation regardless of INR. Treatment with four-factor PCC (prothrombin complex concentrate) is favored over FFP (fresh-frozen plasma, in addition to vitamin K 5 to 10 mg by slow IV injection. If readily available (e.g. at home), patient may take oral vitamin K 5 to10 mg prior to leaving for hospital, but shouldn't delay hospital transport. PCC and FFP work immediately; even IV vitamin K, although having more rapid onset of action than oral vitamin K, takes hours to work.
3. Emergency room evaluation or elevated INRs is generally not required unless the patient is experiencing signs or symptoms of bleeding.
4. If there is very good reason to doubt test results (e.g. short draw of venous INR), recheck INR before taking definitive clinical action. In these circumstances, warfarin should be held until decision is made, and decision should not be deferred to the following day.
5. CHEST-9 and ASH guidelines suggest against use of vitamin K to reverse INR elevations in the 4.5 to 10.0 range, in the absence of bleeding. Although supratherapeutic INRs will return to therapeutic range more rapidly with vitamin K administration, there is no evidence for improvement in important outcomes, such as decrease in major bleeding[54]. However, the suggested approach in CHEST-9 depends on a relative paucity of data acknowledged as imprecise and only of moderate quality. None of the supporting studies separated patients based on bleeding risks or likelihood of persistence of elevated INR due other relevant factors, such as diarrhea, use of continued antibiotics, or alcohol abuse. No study separated low from high-risk patients, thereby diluting potential benefits of treatment for high-risk patients. One study did find short-term benefit for treated patients.[55] Therefore, acknowledging the paucity of supporting (and contrary) evidence, we recommend that patients with an elevated INR 6.0 - 10.0 ***without significant bleeding*** undergo a four-step process, including:

a) Assessment of the clinical context – has patient had recent surgery or other procedure that would increase likelihood of bleeding, recent bleeding under treatment, and/or presence of medications that would significantly increase bleeding risk, such as aspirin and other antiplatelet agents?
b) Determination of bleeding risk score using HAS-BLED (see "Bleeding Risk Score" section below)
c) Assessment for factors that would be expected to interfere with the normal correction of INR by simply holding warfarin, such as continued poor dietary intake, vomiting, diarrhea, or medications that decrease warfarin metabolism
d) Development of plan for patient management, including at minimum holding until INR in range or approaching therapeutic range and close follow-up of the INR.

In general, the consideration driving this decision to use vitamin K with INR 6.0 - 10 without significant bleeding depends on the condition(s) most likely to result in bleeding, such as a recent condition likely to predispose to bleeding (e.g. recent bleeding or invasive procedure), concurrent use of an antiplatelet agent, and/or anticipated prolonged high-INR state despite holding warfarin. When any of these conditions exists, vitamin K should be considered. When all are absent, simply hold warfarin and closely follow the INR per guidance outlined in "Application of Bleeding and Bleeding Risk Assessment to Clinical Scenarios" section below.

6. For patients taking warfarin with INR >10.0 and no evidence of bleeding, oral vitamin K should be administered.
7. For AF in patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, a consult should be submitted to transition patient to apixaban, edoxaban, or dabigatran 110mg (off-label) as all demonstrate significantly less major bleeding compared with warfarin (CHEST-2018).
8. For all patients with AF, use HAS-BLED score to address modifiable bleeding risk factors. Those potentially at high risk (HAS-BLED score ≥3) warrant more frequent and regular reviews and follow-up.

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[54] Khatib R, Ludwikowska M, Witt D, et al. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. *Blood Adv.* 2019;3(5):789-796.

[55] Crowther. MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomized controlled trial. *Lancet.* 2000; 356 (9241): 1551- 1553.

Bleeding Risk Score:

We are now using HAS-BLED to determine bleeding risk scores of our patients; the relevant risk factors are noted below. Bear in mind that there are other available bleeding risk scores, which may consider some factors not in the HAS-BLED tool. CHEST-2012, for example, contains a more comprehensive list of bleeding risk factors, used to compare the relative risks of recurrent thromboembolism and bleeding with extended treatment vs. short-term treatment for VTE. These risk factors should also be taken into consideration in the setting of a high INR:[56] *Note: for patients initiating warfarin therapy, we suggest against the routine use of clinical prediction rules such as bleeding risk scores as the sole criterion to withhold warfarin therapy.*

- Age 65+
- Age 75+
- Alcohol abuse
- Anemia
- Antiplatelet therapy
- Cancer
- Comorbidity and reduced functional capacity
- Diabetes
- Frequent falls
- Liver failure
- Metastatic cancer
- Poor anticoagulant control
- Previous bleeding
- Previous stroke
- Recent surgery
- Renal failure
- Thrombocytopenia

HAS-BLED

Bleeding Risk Factors	Points
Hypertension History (uncontrolled, >160 systolic)	1
Renal disease (Dialysis, transplant, Cr >2.26 mg/dL)	1
Liver disease (Cirrhosis or Bilirubin >2x Normal or AST/ALT/AP >3x Normal)	1
History of Stroke	1
Prior Major Bleeding or Predisposition to Bleeding	1
Labile INR	1
Age > 65 years	1
Medication Usage Predisposing to Bleeding (NSAIDS, antiplatelet agents)	1

[56] Adapted from Kearon et al; Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines - 2012: Table 2 (Section 2.3, 3). Consult original document for further details and explanation of risks.

Alcohol or Drug Usage history (≥8 drinks/week)	1

HAS-BLED Score	Risk of Bleeding in 1 year	Bleeding Risk Category
0	Risk was 0.9% in one validation study and 1.13 bleeds per 100 patient-years in another validation study.	Low
1	Risk was 3.4% in one validation study and 1.02 bleeds per 100 patient-years in another validation study.	Low
2	Risk was 4.1% in one validation study and 1.88 bleeds per 100 patient-years in another validation study.	Moderate
3	Risk was 5.8% in one validation study and 3.72 bleeds per 100 patient-years in another validation study.	High
4	Risk was 8.9% in one validation study and 8.70 bleeds per 100 patient-years in another validation study.	High
5	Risk was 9.1% in one validation study and 12.50 bleeds per 100 patient-years in another validation study.	High
6	Scores greater than 5 were too rare to determine risk, but expected to be high based on high risk with score of 5.	Very High
7	Scores greater than 5 were too rare to determine risk, but expected to be high based on high risk with score of 5.	Very High
8	Scores greater than 5 were too rare to determine risk, but expected to be high based on high risk with score of 5.	Very High
9	Scores greater than 5 were too rare to determine risk, but expected to be high based on high risk with score of 5.	Very High

Application of Bleeding and Bleeding Risk Assessment to Clinical Scenarios[57]:

Clinical Scenario I: Patient is bleeding:

INR	Bleeding Risk Category	Guideline Plan:
Minor bleeding with INR ≥ 5.0	*All: critical actions*	• **Notify PCP or other physician on the patient's care team or covering system of the INR and clinical description of bleeding.** • **PCP or other physician on the patient's care team or covering system advises clinical action if evaluation or other action required[58].** • **Omit the next dose or two and monitor INR before making additional adjustments; resume therapy at lower dose when the INR is within or approaching therapeutic range and clinically appropriate.**
Serious and/or life-threatening bleeding, regardless of INR	*All: critical actions*	• **Immediately contact PCP and send patient to emergency room.** • **Notify PCP or other physician on the patient's care team or covering system.**

Clinical Scenario 2: Patient is not bleeding, but has INR 6.0 – 10

Clinical context	Guideline Plan:
• All	• **CONSULT NEEDED: Report indication/target range, INR, bleeding risk, presence of anti-platelet agent, and presence of other relevant clinical circumstances to a consultant to assess need for vitamin K administration (see "Use of Vitamin K" section below).** • If Vitamin K used: hold warfarin and retest INR within 24 hours • If Vitamin K NOT used: hold warfarin for 2 to 3 days prior to checking INR • Once INR is within or approaching therapeutic range, resume warfarin therapy and reduce weekly dose by 20% to 50% as directed by consultant • Monitor INR every 3 to 4 days for at least 1 week

Clinical Scenario 3: Patient is not bleeding, but has INR > 10:

[57] Guideline plans are color-coded for easy reference, including:
- **Red text: Required consultation with PCP or other physician on the patient's care team or covering system, or a thrombosis CDTM authorized pharmacist before taking clinical action.**
- **Green text: Notification of PCP or other physician on the patient's care team or covering system after taking clinical action.**

[58] Examples of minor bleeding include lacerations with oozing that stops with pressure, nosebleed that stops quickly with pressure, blood to toilet paper. Onsite evaluation is recommended whenever bleeding is not obviously minor.

Clinical context	Guideline Plan:
• All	• **CONSULT NEEDED: Report indication/target range, INR, bleeding risk, presence of anti-platelet agent, and presence of other relevant clinical circumstances to a consultant. Vitamin K is indicated at dose of 2.5mg to 5mg (see "Use of Vitamin K" section below).** • Report intervention to PCP or other physician on the patient's care team or covering system, who may recommend additional medical evaluation (if indicated, the Anticoagulation manager or PCP will make arrangements for obtaining this evaluation). • Notify PCP of high INR and above intervention. • Retest INR within 24 hours of vitamin K administration • Once INR is within or approaching therapeutic range, resume warfarin therapy and reduce weekly dose by 20% to 50% as directed by consultant • Monitor INR every 3 to 4 days for at least 1 week (starting with the day after vitamin K administration)

Use of Vitamin K:

- The following recommendations are for reversal of excessive anticoagulation due to warfarin (INR > 6.0) without active bleeding
- Patients with a compelling indication should generally receive vitamin K. **INR should be tested within 24 hours of vitamin K administration.**
- Patients who have any of the exclusion criteria outlined below should generally not receive vitamin K due to risk of INR overcorrection and high risk of thrombosis
- Use of vitamin K in a clinical scenario where the patient has both a compelling indication and any exclusion criteria will require individualized assessment of bleeding and clotting risks on a case by case basis
- Vitamin K[1] should be used over vitamin K[2] as this was the type of vitamin K assessed in clinical trials[59]
- Use of over-the-counter sources of vitamin K may be limited by the variable quality and amount of active-ingredient contained in available formulations[60]
- Re-dosing of vitamin K should be avoided unless repeat INRs are higher than the index result or if INR begins to trend upwards again without readministration of warfarin in order to limit INR overcorrection[61,62]

[51] Khatib R, Ludwikowska M, Witt D, et al. Vitamin K for reversal of excessive vitamin K antagonist anticoagulation: a systematic review and meta-analysis. *Blood Adv.* 2019;3(5):789-796.
[60] Witt D, Nieuwlaat R, Clark N, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. *Blood Adv.* 2018: 2(22):3257-3291.
[53] Baker P, Gleghorn A, Tripp T, et al. Reversal of asymptomatic over-anticoagulation by orally administered vitamin K. *Br J Haematol* 2006;133(3):331-336.
[54] Chirputkar SK, Poole JH, McNeil RC, et al. Reversal of asymptomatic over-anticoagulation with oral Vitamin K. Br J Haematol 2006;135(4):591-592

Compelling Indications[45,47,63] (Vitamin K Generally Advised)	Compelling Exclusion Criteria (Vitamin K Generally Avoided)

• INR > 10.0
• Concomitant use of ASA or other antiplatelet drugs
• Surgery within 2 weeks
• Major bleeding within previous 4 weeks
• Platelets < 50K
• Known liver disease
 	
Presence of any factors that would result in prolonged high INR state[64]:
 	
• Age ≥ 75 with weekly warfarin dose of ≤ 15mg
• Decompensated heart failure - defined as primary diagnosis for hospitalization within 14 days
• Active cancer - defined as treatment with chemotherapy or metastatic disease
• Recent initiation of CYP2C9/3A4 inhibitor such as amiodarone, ciprofloxacin, cimetidine, fluconazole, clarithromycin, erythromycin, metronidazole, or sulfamethoxazole/trimethopr
	• VTE within 3 months
	• Previous history of VTE at therapeutic or nearly-therapeutic INRs
	• History of recurrent VTE due to defined condition still present
	• High risk thromboembolic history as defined as one of the following:
	  ○ One unprovoked event plus antiphospholipid syndrome or deficiencies of antithrombin, protein C, or protein S
	  ○ Recurrent unprovoked events plus any other thrombophilia
	  ○ Singular unprovoked life-threatening event like massive near fatal PE
	  ○ One unprovoked event at unusual site such as cerebral, mesenteric, or portal vein
	• AF with CHA2DS2-VASc Score of ≥ 7 or with CVA within 3 months
	• High risk valvular disease as defined as one of the following:
	  ○ Any mechanical valve in the mitral position
	  ○ Any caged ball or tilting disk valve with INR goal of 2.5 – 3.5
	  ○ Rheumatic mitral stenosis
	  ○ Any mechanical valve and CVA within 6 months
	  ○ Multiple mechanical valves
	• Inability to retest INR within 24 hours of vitamin K administration

[63] Tran H, Chunilal S, Harper P, et al. An update of consensus guidelines for warfarin reversal. *Med J Aust* 2013;198(4): 198-199.

[64] Hylek E, Regan S, Go A, et al. Clinical Predictors of Prolonged Delay in Return of the International Normalized Ratio to within the Therapeutic Range after Excessive Anticoagulation with warfarin. *Ann Intern Med* 2001;135:393-400.

INR	Vitamin K PO Dose	Anticipate Effects of Dose
6.0 – 7.9	1mg	• 1mg dose produces approximate INR reduction of 2.8 to 4.7 INR units within 1 day[65,66] and leads to both lower mean INR and greater number of patients with INR < 5.0 for index INRs up to 12.0[58] • Rate of INR overcorrection (INR < 2.0 after 24 hours) range from 10% to 36.6%[58,67]
8.0 – 10	1mg to 2.5mg	• 2.5mg dose produces approximate INR reduction of 4.8 to 5.4 INR units within 1 day[53,68,69] • 2.5mg dose reduces time to reach INR < 4.0 by about 1 day for index INRs < 10 compared to holding warfarin alone[60] • Rate of INR overcorrection (< 2.0 within 24 hours) with 2.5mg dose is 8% for patients with index INR of 8.0 – 11.9[54]
≥ 10	2.5mg to 5mg	• 5mg dose produces approximate INR reduction of approximately 11 INR units within 1 day[53] • Rate of INR overcorrection (< 2.0 within 24 hours) with 5mg dose is approximately 17% to 29% even when used for INRs > 12.0[53] • 5mg doses are effective at reducing INR quickly even at INR values > 21.0[53] • No reported issues with warfarin resistance associated with Vitamin K doses up to 5mg[51]
		• **Holding warfarin without vitamin K administration at INR values > 4.5 results in approximate INR reduction of 1.0 to 2.5 INR units within 24 hours[57,58]** • **Higher index INR will result in greater INR drop once warfarin is withheld (vitamin K has more profound impact at higher INRs as well)[58]**

[65] Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomised controlled trial. Lancet. 2000;356:1551-1553.

[66] Ageno W, Garcia D, Silingardi M, et al. A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves. J Am Coll Cardiol. 2005;46(4):732-733.

[67] Ageno W, Crowther M, Steidl L, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a randomized controlled trial. *Thromb Haemost* 2002;88(1):48-51.

[68] Patel RJ,Witt DM, Saseen JJ, et al. Randomized, placebo-controlled trial of oral phytonadione for excessive anticoagulation. Pharmacotherapy. 2000;20:1159-1166.

[69] Lubetsky A, Yonath H, Olchovsky D, et al. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med. 2003; 163:2469-2473.

Appendix 6: MANAGING PATIENTS WITH LOW INR VALUES

Anticoagulation Manager Management of Unplanned Lows:

1. Try to determine the reason for low INR.
    a) **Dosing:** Is patient taking the correct dose? Have patient tell you the dose he/she is taking. Look for warfarin prescription in medication history.
    b) **Missed pills:** Has patient missed any doses? If so, how many days and how long ago?
    c) **Meds:** Has patient started, stopped, or changed any other medications (including herbals)? Look in medication history.
        i. Check for changes:
            1) Check medication list.
            2) Review outside sources if additional information is noted in Snapshot or Problem List (for example, checking Web Portal)
            3) Ask patient.
        - Medications to consider:
            1) Inducers lower INR levels (speed up the metabolism of warfarin). Did patient START an inducer, such as phenytoin, phenobarbital, rifampin, or carbamazepine?
            2) Inhibitors raise INR levels (slow down the metabolism of warfarin). Did patient STOP or decrease the dose of acetaminophen, amoxicillin, amiodarone, fibrates, quinolones (ciprofloxacin, levofloxacin), cimetidine, fluconazole, clarithromycin, erythromycin, metronidazole, or sulfamethoxazole/trimethoprim?
    d) **Diet:** Has patient increased vitamin K in diet (e.g. more dark, green leafy vegetables)?
    e) **OTC medications or supplements:** for example, has patient begun or increased intake of green tea or ginseng?
    f) **Alcohol:** Has patient decreased alcohol consumption?

    Note: If patient was previously stable and no cause can be found, the most likely cause is missed pills.

2. Assess whether the patient has a stable vs. "active management" regimen.
    - **Stable regimen:** A patient is considered stable if s/he has **two therapeutic INR's in two successive months** without a change in warfarin dosing. A stable patient who develops a single, unplanned low INR is at fairly low risk of complications.
    - **"Active management" regimen:** A patient is not stable and considered in "active management" if his/ her warfarin dose is being titrated or if s/he has had an INR that was out of therapeutic range on either of the last two readings.
        - If a stable patient has a low INR, bridging is generally not required.
        - If the same patient returns for follow up and has *a second low INR*, s/he is now in "active management" and not stable.

3. Determine whether change in warfarin is indicated.
    - **<u>Stable regimen, transient low:</u>** If a patient has missed dose(s) or taken incorrect dose(s), or if the low INR seems to be due to medications or dietary changes that no longer are present (e.g. harvested the spinach crop, but now sick of spinach), then the patient should resume prior dosing.
        - If INR is more than 0.5 below target range (for example, if target range 2.0-3.0, more than 0.5 below target range will be a value of ≤1.4)→advise patient to take double the usual nightly dose for 1-2 days, depending on the extent of INR decrease, usual dose of the patient, and number of missed doses, if known.
        - If INR is within 0.5 below the target range (e.g., in the above situation, 1.5-1.9)→ continue usual regimen after making up 1-2 missed dose(s).

  - Regardless, recheck INR in 1-2 weeks.
  - Bridging is not usually needed unless patient is at high or very high risk of clotting (e.g. two mechanical prosthetic valves, atrial fibrillation with CHA2DS2-VASc score of ≥7 and/or recent stroke and/or is in early management stage of acute venous thrombosis [e.g. DVT/PE within 3 months]); consult with the consultant in these circumstances. Bridging may also be considered in the presence of other high-risk conditions, such as a history of a prior event while on treatment with a subtherapeutic INR, or in some situations with high-risk thrombophilia. See *Thromboembolic Risk Assessment* table for full list.
- **Stable regimen, new circumstances:** If a stable patient has changed medication, diet, or alcohol consumption, and this change is expected to continue, his/her regimen will need adjustment.
  - Adjust warfarin dosing and monitor INR response per *Appendix 3: Guidelines for Maintenance Dose Adjustment and Monitoring*.
  - If patient is not at goal at 1st recheck, assess as an "active management" patient.
- **Active management regimen:**
  - Adjust warfarin dosing and monitor INR response per *Appendix 3: Guidelines for Maintenance Dose Adjustment and Monitoring*.
  - If INR is more than 0.2 below target range (e.g. for above situation, INR below 1.8), anticoagulation manager will assess the patient's risk and recommend bridging with LMWH/Fondaparinux if appropriate based on *Thromboembolic Risk Assessment*.

4. Consult with a consultant as advised in *Thromboembolic Risk Assessment* or other situations when treatment decision is not straightforward; notify PCP when directed by the consultant

5. Arrange LMWH/Fondaparinux when appropriate.
   - If a bridging medication is necessary, The AMS manager will order the medication and route to PCP for approval.
   - Notify PCP to arrange self-injection teaching, when required, or to make alternative arrangements, such as nursing visits or office visits when needed. AMS can assist in the process, but the injections are the PCP's responsibility.
   - Discontinue LMWH/Fondaparinux when the INR has returned to therapeutic range.

Anticoagulation Manager Management of Planned Lows:

- If oral anticoagulation is held for a scheduled procedure, the Anticoagulation manager will assess risk in advance and recommend bridging with LMWH/Fondaparinux therapy when appropriate. Stability of INR values does not affect recommendations to bridge before procedures.
- If there are special considerations, the Anticoagulation manager will review the case with the consultant, and the consultant will make treatment recommendations.
- The Anticoagulation manager will submit all hold plans to the PCP and the surgeon/physician performing the procedure for final approval.
- The Anticoagulation manager will recommend resuming anticoagulation per *Appendix 7: General Recommendations for Perioperative Anticoagulation: When can anticoagulation restart?*
- When re-starting warfarin, the Anticoagulation manager will initiate warfarin at a dose to 1.5 to 2 times usual dose for up to three days to quickly bring INR back into range (and thus minimize the number of days receiving LMWH, if indicated), unless there are specific reasons to avoid higher dosing.
  - If dose is increased, the Anticoagulation manager will note "increase beyond usual dose" in the Anticoagulation Tracker to alert AMS and on-call providers of the need to reduce dose to usual level once INR reaches goal range.
- INRs are monitored in accordance with usual guidelines.
- The Anticoagulation manager discontinues LMWH/Fondaparinux once the INR is in therapeutic range.

- If the patient is not bridging with LMWH/Fondaparinux and is at low thromboembolic risk, it is generally acceptable to resume patient on his/her previous STABLE dose when approved by the clinician performing the procedure. The INR can then be checked again in 2-4 weeks, depending on the previous stability of the INR.

Recommendations for LMWH (Enoxaparin or Dalteparin) / Fondaparinux dosing, when required:

Enoxaparin (Lovenox®), LMWH:
Full Dose:

- First choice: LMWH 1 mg/kg SC twice daily.
- Second choice: LMWH 1.5 mg/kg SC once daily.

Prophylactic Dose:

- DVT prophylaxis in abdominal surgery 40 mg SC once daily
- DVT prophylaxis in knee replacement surgery 30 mg SC every 12 hours
- DVT prophylaxis in hip replacement surgery 30 mg SC every 12 hours or 40 mg SC once daily
- DVT prophylaxis in medical patients 40 mg SC once daily

Prophylactic dosing regimens have generally not been weight based; however, standard doses of enoxaparin (40 mg daily or 30 mg twice daily) in morbid obesity can lead to plasma concentrations that are generally considered to be subtherapeutic.

- For patients with a BMI ≥40 kg/m^2 and CrCl >30 mL/min, enoxaparin 40 mg subcutaneously twice daily has been a suggested prophylactic dose.[70]
- In patients with extreme obesity (BMI ≥50 kg/m^2), doses of enoxaparin may need to be even higher. Based on data from a single trial, practitioners may consider doses as high as 60 mg twice daily in this population, although more studies need to be done before this should be broadly implemented in clinical practice.[1]

Dosage Regimens for Patients with Severe Renal Impairment (creatinine clearance <30 mL/minute):

- Prophylaxis in abdominal surgery 30 mg administered SC once daily
- Prophylaxis in hip or knee replacement surgery 30 mg administered SC once daily
- Prophylaxis in medical patients during acute illness 30 mg administered SC once daily
- Treatment of DVT with or without PE 1 mg/kg administered SC once daily

Some experts have recommended against the use of LMWH in patients with CrCl <20 mL/min.[71]

[70] Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. J Thromb Thrombolysis. 2016; 41(3):475-81.
[71] Smythe MA, Priziola J, Dobesh PP, Wirth D, Cuker A, Wittkowsky AK. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016 01/16; 41:165-86.

Hemodialysis patient: LMWH not recommended; per CHEST-9 recommendations, use weight-based subcutaneous unfractionated heparin (333 units/kg, then 250units/kg twice daily); although aPTT monitoring is not usually advised, it should be considered for obese patients or in situations requiring prolonged bridging. Note that the quality of evidence supporting bridging recommendations for patients with ESRD is of poor quality.[72]

Fondaparinux (Arixtra®):

Full Dose:

a. If patient weighs <50 kg, Fondaparinux 5 mg SC once daily.
b. If patient weighs 50-100 kg, Fondaparinux 7.5 mg SC once daily.
c. If patient weighs >100 kg, Fondaparinux 10 mg SC once daily.

Prophylactic Dose

- Fondaparinux 2.5 mg SC once daily; dose is not weight-based.
- Prophylactic dosing contraindicated in patients with body weight <50 kg

For patients with a BMI ≥40 kg/m^2: Since there is better data with enoxaparin and UFH in this population, these agents preferred unless contraindicated. When using fondaparinux, standard doses of 2.5 mg daily recommended until more evidence emerges to support higher dosage regimens.[73]

Special considerations for renal dose adjustment:

- CrCl 50-80 mL/min: 25% reduction in total clearance; no dosage adjustments provided in the manufacturer's labeling.
- CrCl 30-50 mL/min: 40% reduction in total clearance; use with caution; no dosage adjustments provided in the manufacturer's labeling; when used for thromboprophylaxis, the American College of Chest Physicians (2012) suggests a 50% reduction in dose or use of low-dose heparin instead of fondaparinux.[74]
- CrCl <30 mL/min: use contraindicated.

Bridging considerations:

- The half-life of Arixtra (fondaparinux) is 17-21 hours, so anticoagulant activity may continue for up to six days, depending on the specific patient context, including renal function. We recommend against its routine use in most bridging situations.
- With certain precautions, it may be used in the following circumstances, after review with a consultant:
  1. Perioperative bridging of patients with history of HIT, where LMWH and UFH is contraindicated, who would otherwise require inpatient care for alternative management options.
  2. Perioperative bridging of patients with antithrombin deficiency, since LMWH and UFH are ineffective as anticoagulants.
- When used in patients with normal renal function, the last dose should be administered at least two days before low-bleeding-risk surgery and four days before procedures that have a high risk of bleeding.
- When used in patients with mild kidney dysfunction (creatinine clearance 30-50 mL/min), last dose should be administered four to six days before the procedure. This approach may be impractical in most situations, since it approximates the hold time of warfarin.

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[72] Chest-2012-Holbrook-Evidence-Based Management of Anticoagulant Therapy -e152S-84S.
[73] Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. J Thromb Thrombolysis. 2016; 41(3):475-81.
[74] Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012 02/01; 141(2):e24S-43S.

- Fondaparinux (Arixtra) should never be used for bridging in patients with creatinine clearance below 30 or for procedures with very high risk of bleeding, such as spinal surgery or neuroaxial catheter placement.[75]

Dalteparin (Fragmin®):

Condition	Dose
Abdominal surgery (DVT prophylaxis):	
Low to moderate DVT risk	2500 IU 1-2 hours prior to surgery, then once daily for 5-10 days postoperatively
High DVT risk	5000 IU the evening prior to surgery, then once daily for 5-10 days postoperatively
Malignancy	2500 IU 1-2 hours prior to surgery and 12 hours later, then 5000 IU once daily for 5-10 days postoperatively.
Total hip surgery (DVT prophylaxis) options:	*Note: delay post-op dosing until hemostasis is achieved.*
Postoperative start	Initial: 2500 IU 4-8 hours after surgery. Maintenance: 5000 IU once daily; start at least 6 hours after postsurgical dose
Preoperative (starting day of surgery):	Initial: 2500 IU within 2 hours before surgery then 2500 IU 4-8 hours* after surgery. Maintenance: 5000 IU once daily; start at least 6 hours after postsurgical dose
Preoperative (starting evening prior to surgery)	Initial: 5000 IU 10-14 hours before surgery. 5000 IU 4-8 hours***** after surgery. Maintenance: 5000 IU once daily, allowing 24 hours between doses.
Other indications:	
Unstable angina or non-Q-wave myocardial infarction:	120 IU/kg body weight up to 10,000 IU every 12 hours for 5-8 days with concurrent aspirin therapy; Discontinue dalteparin once patient clinically stable.
Extended VTE treatment in Cancer patients	Month 1: • ≤124 pounds (≤56kg): 10,000 IU once daily • 125-150 pounds (57 to 68 kg): 12,500 IU once daily • 151-181 pounds (69 to 82 kg): 15,000 IU once daily • ≥182 pounds (≥ 83 kg): 18,000 IU once daily Months 2-6: • ≤124 pounds (≤56kg): 7,500 IU once daily • 125-150 pounds (57 to 68 kg): 10,000 IU once daily • 151-181 pounds (69 to 82 kg): 12,500 IU once daily • 182-216 pounds (83 to 98 kg): 15,000 IU once daily • ≥217 pounds (≥ 99 kg): 18,000 IU once daily

[75] Garwood, C et al; Is there a Role for Fondaparinux in Perioperative Bridging? Am J Health Syst Pharm. 2011;68(1):36-42

	Note: if platelet count between 50,000-100,000/mm^3, reduce dose by 2,500 IU until platelet count recovers to ≥100,000/mm^3; if platelet count <50,000/mm^3, discontinue dalteparin until platelet count recovers to >50,000/mm^3. In patients with severely impaired renal function (CrCl < 30 mL/min), monitoring for anti-Xa levels is recommended to determine the appropriate dose. Target anti-Xa range is 0.5–1.5 IU/ml. When monitoring anti-Xa in these patients, sampling should be performed 4–6 hours after dosing and only after the patient has received 3-4 doses.
Immobility/acute illness (DVT prophylaxis):	5000 IU once daily

*Table adapted from **DRUGDEX®***

For patients with a BMI ≥40 kg/m^2 and CrCl >30 mL/min: consider using enoxaparin instead. If unable to substitute, consider increasing total daily dose of dalteparin by 25–30%.[76]

Anticoagulation of morbidly obese patients: Pharmacodynamic studies have indicated safety and efficacy for weight-based recommendations of LMWHs at the following levels: enoxaparin (Lovenox) **-** up to 144 kg (BMI ≤48); dalteparin (Fragmin) - up to 190 kg (BMI ≤58; tinzaparin (Innohep) - up to 165 kg (BMI ≤61)[77]

[76] Vandiver JW, Ritz LI, Lalama JT. Chemical prophylaxis to prevent venous thromboembolism in morbid obesity: literature review and dosing recommendations. J Thromb Thrombolysis. 2016; 41(3):475-81.

[77] Domienik-Karlowicz, J and Pruszczyk, P. The use of anticoagulants in morbidly obese patients; Cardiology Journal, 23;1; 2016; p 12-13

Venous Thromboembolic Risk Assessment:[78]

Risk Category for venous thromboembolic event	Examples in risk category (note that some categories do not require anticoagulation, but are best treated with anti-platelet agents)	Yearly risk (%), if known	Recommendations for anti-thrombotic treatment	Recommendation for bridging for low INR. Consult needed before bridging a patient who has had a major bleed within 3 months, or prior bleed from bridging, or who has quantitative or qualitative platelet abnormality including aspirin use. Bridging is NOT recommended for patients on DOACS.
NORMAL RISK	• **Patients with heterozygous factor V Leiden mutation but no history of DVT/PE.** These patients have the same risk for an initial thrombotic event as the rest of the general population, and do not need prophylaxis beyond what would be provided to other normal-risk patients.		No treatment needed.	
LOW RISK, VTE prophylaxis	• **DVT/PE >3 months ago and no other risk factors**	<4	Treat with warfarin or DOAC when indicated	• Consider bridge with prophylactic dose for: - Post-operative period if immobility or casting expected during return to therapeutic INR - Warfarin hold with expected immobility or casting - Any other circumstance which poses similar risk. • Bridge not recommended for: - INR ≥1.5 - Incidentally-discovered subtherapeutic INR with expected return to therapeutic range within a week - Procedural or operative holds with expected normal mobility post-op. • For surgery, bridge should generally be post-operative only.
	• **Patients anticoagulated due to pulmonary hypertension, in absence of history of thromboembolic disease** (if history of thromboembolic disease, risk generally relates to specific history of thromboembolic disease, not to the risk of pulmonary hypertension)			
MODERATE RISK VTE prophylaxis	• **History of <u>recurrent</u> DVT/PE > 3 months, due to specific condition no longer present, or no clear risk factor**	Not quantified	Treat with warfarin or DOAC (except LMWH or DOAC generally preferred in active cancer)	• Consider bridge with prophylactic dose for: - Post-operative period if immobility or casting expected during return to therapeutic INR - Any warfarin hold with expected immobility or casting - Any other circumstance which poses similar risk. • Bridge not recommended for: - INR ≥1.5 - Incidentally discovered subtherapeutic INR with expected return to therapeutic range within a week - Procedural or operative holds with expected normal mobility post-op. • For surgery, bridge should generally be post-operative only.
	• **History of DVT/PE in the presence of heterozygous factor V Leiden or prothrombin gene mutation, with either an additional thrombophilic defect or when the prior episode was unprovoked, > 3 month**			
	• **DVT/PE with active cancer (treated within 6 months or palliative stage)**			

HIGH RISK – VTE treatment	• **DVT/PE within 3 months - Treatment**		Treat with warfarin or DOAC (warfarin preferred in setting of antiphospholipid syndrome)	• Postpone procedures requiring VKA hold when possible. • Bridge with treatment dose for the following: - INR <1.5 or more than 0.5 below low end of target range, or - INR <1.8 in the first month following clot onset - Any planned hold. • Consider bridging for INR 1.5-1.7 in the second and third months of treatment in the case of extensive clot • For holds, include pre and post-operative bridge. • For high bleeding risk (defined above), consider prophylactic dosing for bridge.
HIGH RISK – VTE prophylaxis	• **History of DVT/PE in the setting of a therapeutic or nearly-therapeutic INR, > 3 months**		Treat with warfarin or DOAC (warfarin preferred in setting of antiphospholipid syndrome)	• Bridge with treatment dose for the following: - INR <1.5 or more than 0.5 below low end of target range, or - Any planned hold. • For holds, include pre and post-operative bridge. • For high bleeding risk (defined above), consider prophylactic dosing for bridge.
	• **A history of recurrent DVT/PE, due to defined condition still present**	20+		
	• **High risk thrombophilia, defined as one of the following:** a. One spontaneous event plus antiphospholipid syndrome[79], deficiency of antithrombin, protein C, or protein S, or multiple abnormalities b. Two or more spontaneous events plus any of other causes of thrombophilia except as in "a" c. One spontaneous life threatening event like massive near fatal PE, or cerebral, mesenteric or portal vein thrombosis d. One spontaneous event at unusual site, such as cerebral, mesenteric or portal vein regardless of presence of genetic factor for thrombophilia, in the absence of a provoking cause that has resolved	20+		

[78] Originally adapted from Dunn, A.S. and Turpie, A.G., *Perioperative Management of Patients Receiving Oral Anticoagulation Therapy*, Archives of Internal Medicine, Vol 163, April 28, 2003, and revised in accordance with CHADS2 data and CHEST-9 recommendations; original table updated in accordance with updated guidelines-4/03/2019

[79] Anti-phospholipids include lupus anticoagulants, anticardiolipin antibody, and antiphospholipid antibody. See **Appendix 9** for review.

Arterial Thromboembolic Risk Assessment:[80]

Risk Category for arterial thromboembolic event	Examples in risk category (note that some categories do not require anticoagulation, but are best treated with anti-platelet agents)	Yearly risk (%), if known	Recommendations for anti-thrombotic treatment	Recommendation for bridging for low INR. Consult physician before bridging a patient who has had a major bleed within 3 months, or prior bleed from bridging, or who has quantitative or qualitative platelet abnormality including aspirin use. Bridging is NOT recommended for patients on DOACS.
LOW SHORT-TERM RISK of Arterial Thromboembolic Event (consultation with consultant not required)	• Lone atrial fibrillation (no co-morbidities and age <65; male; CHA2DS2-VASc = 0	0.2-0.3	• 2014 AHA/ACC/HOURS: Reasonable to omit antithrombotic therapy • 2016 ESC: No antiplatelet or anticoagulant treatment recommended (Note: only use anticoagulant or aspirin 81-325 mg daily if strong patient preference after risk-benefit discussion)[81]	• If anticoagulated, bridging not recommended when withholding warfarin temporarily or for incidentally-discovered low INR's.
	• Lone atrial fibrillation (no co-morbidities and age <65; female; CHA2DS2-VASc = 1 (per ESC guideline))	0.6-0.9		
	• Atrial fibrillation; CHA2DS2-VASc = 1 • Atrial fibrillation (age = <75; female CHA2DS2-VASc = 2 (per ESC guideline))	0.6-0.9 2.2-2.9	• Oral anticoagulation should be considered, taking into account individual characteristics and patient preferences (antiplatelet therapy <u>not</u> recommended) (ESC-2016) • Oral anticoagulation should be offered to patients with one or more non-sex CHA2DS2-VASC risk factors (score ≥1 for males, ≥2 for females); regardless of stroke risk, antiplatelet agents alone not recommended for stroke prevention (CHEST-2018); also supported by ACC/AHA/HRS-2019)	

[80] Originally adapted from Dunn, A.S. and Turpie, A.G., Perioperative Management of Patients Receiving Oral Anticoagulation Therapy, Archives of Internal Medicine, Vol 163, April 28, 2003, and revised in accordance with CHADS2 data and CHEST-9 recommendations; updated to current guidelines as of April 3, 2019.

[81] New referrals for lone atrial fibrillation require documentation of risk-benefit discussion with patient. For long-term anticoagulation, reduction of cardioembolic strokes with warfarin vs. aspirin in this risk group is approximately 3:1000 patients/year, generally considered too low to warrant treatment with anticoagulation vs. aspirin. This consideration does not apply when cardioversion is anticipated or planned; in these situations, warfarin is always required.

	• Atrial fibrillation with risk factors; CHA2DS2-VASc = 2-4, without history of embolic stroke or TIA, or systemic embolization CHA2DS2-VASc = 2 CHA2DS2-VASc = 3 CHA2DS2-VASc = 4	 2.2-2.9 3.2-4.6 4.8-6.7	Treat with anticoagulant (DOAC or warfarin)	
	• Cardiomyopathy without atrial fibrillation	<4	May treat with long-term warfarin if very low EF, history of LV thrombus, or localized akinetic areas; criteria for anticoagulation not well-established; see footnote on WARCEF trial[82]	
	• Rheumatic mitral valve disease (stenosis and regurgitation; risk 1.5 times higher in stenosis) in absence of atrial fibrillation	<5	Treat with aspirin 325 mg if LA <5.5cm Treat with warfarin if LA ≥5.5cm	
	• Aortic or mitral tissue valve (>6 months after placement)	<4	Treat with aspirin 81-325 mg daily	
	• Bileaflet mechanical aortic valve prosthesis without AF, prior thromboembolism, left ventricular dysfunction, or hypercoagulable state)	<4	Treat with warfarin	
MODERATE SHORT-TERM RISK of Arterial Thromboembolic Event (consultation with consultant suggested when decision unclear)	• Atrial fibrillation with prior embolic stroke within 3 days of holding warfarin		Treat with anticoagulant (DOAC or warfarin)	• Bridge with treatment dose for the following: - Incidental lows <1.5 or more than 0.5 below lower end of therapeutic range - All planned holds. • Post-op, initiate as soon as possible based on bleed risk and surgeon's clearance.
	• Atrial fibrillation with prior embolic stroke, TIA or systemic embolization CHA2DS2-VASc <=6	2.2-13.6	Treat with anticoagulant (DOAC or warfarin)	• Bridge with treatment dose for the following: - All planned holds - Post-op, initiate as soon as possible based on bleed risk and surgeon's clearance. • Bridging not recommended for incidental lows.
	• Atrial fibrillation with CHA2DS2-VASc = 5 or 6, but NO history of clearly-embolic stroke or TIA or systemic embolization	7.2-13.6	Treat with anticoagulant (DOAC or warfarin)	• Bridging not recommended for incidental lows, surgery or other planned holds.
	• All bioprosthetic valves up to 6 months after placement, without post-placement clot. (See high risk for embolization or left atrial clot within 1st month.) Note, mitral bioprosthetic valve carries higher risk than for aortic bioprosthetic valve.[83]	≤40	**Treat with warfarin if permitted by bleeding risk; otherwise use antiplatelet.**	• Bridging not recommended for incidental lows, surgery or other planned holds. Note: For incidental INR <1.8, if not on antiplatelet agent, start ASA 81 mg and continue until securely back in target range.
HIGH SHORT-TERM RISK of Arterial Thromboembolic Event (consultation with consultant not required)	• **All mechanical valves, first 3 months after placement (see AVR note above)**	≤40	Treat with warfarin	
	• **History of stroke, TIA, or systemic embolization during first month post valve replacement**	Not quantified		

	• **History of embolic stroke, TIA or systemic embolization in the setting of a therapeutic INR.** This includes patients whose INR was within 0.3 of the low end of target range at the time of the event, and patients whose INR was uncertain but thought to have been in the therapeutic range in the 2-3 days before the event.			• Bridge with treatment dose for the following: - Incidental lows <1.5 or more than 0.5 below lower end of therapeutic range - All planned holds. • Initiate post-operative anticoagulation as soon as possible based on bleed risk and surgeon's clearance • For high bleeding risk (defined above), consider prophylactic dosing for bridge.
	• **Aortic caged ball (Starr-Edwards) or tilting disk (Bjork-Shiley) valve (valves with INR goal 2.5-3.5), regardless of additional risk factors**	Not quantified		
	• **Mechanical mitral valve; e.g. St. Jude bileaflet valve (with or without risk factor**	~22[84]		
	• **Atrial fibrillation with rheumatic valvular heart disease (especially mitral valve disease, particularly mitral stenosis)**	>10		
	• **Any mechanical heart valve and recent (within 6 months) stroke or TIA**	>10		
	• **Bileaflet aortic mechanical valve and one of following risk factors: AF, prior thromboembolism, left ventricular dysfunction, or hypercoagulable state[85]**	Not quantified		
	• ***Atrial fibrillation with CHA2DS2-VASc score = 7-9***	11.2-17.4	Treat with anticoagulant (DOAC or warfarin)	
	• **Atrial fibrillation plus prior ischemic stroke, TIA, or systemic embolism within 3 months**	Not quantified	Treat with anticoagulant (DOAC or warfarin)	
HIGHEST SHORT-TERM RISK of Arterial Thromboembolic Event (consultation with a consultant not required)	• **Multiple St Jude's (or other mechanical valves)**	91	Treat with warfarin	• Bridge with treatment dose for the following: - Incidental lows <1.5 or more than 0.5 below lower end of therapeutic range - All planned holds. • Initiate post-operative anticoagulation as soon as possible based on bleed risk and surgeon's clearance • For high bleeding risk (defined above), consider prophylactic dosing for bridge.

Comments: risk of stroke in AF:

- Risk of stroke increases as INR decreases: odds of stroke double at INR of 1.7 and triple at INR of 1.5 compared to INR of 2.0.
- Severity of stroke decreased when stroke occurs with INR in range 2.0-3.0.
- There is no major benefit from increasing INR to top of therapeutic range.
- Definite increase in risk of severe hemorrhage at INR >4.0.

Comments: risk of stroke in patients with prosthetic tissue valves, <u>after the first three months following placement</u>:

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[82] Warfarin and aspirin in patients with heart failure and sinus rhythm. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, Mohr JP, Massie BM, Labovitz AJ, Anker SD, Lok DJ, Ponikowski P, Estol CJ, Lip GY, Di Tullio MR, Sanford AR, Mejia V, Gabriel AP, del Valle ML, Buchsbaum R, WARCEF Investigators; N Engl J Med. 2012;366(20):1859.

[83] Risk at least 5.9% over 3 months, and annualized risk based on first month may be as high as 40% for patients with bioprosthetic valves in mitral position. Therefore LMWH/Fondaparinux preferred over aspirin if INR subtherapeutic, unless subtherapeutic period very brief. .

[84] Figure of 22% refers to annualized risk for St Jude bileaflet valve

[85] Anticoagulation for Valvular Heart Disease; Carnicelli, Anthony. Journal of the American College of Cardiology; 5/18/2015

- Risk of stroke in the absence of atrial fibrillation is categorized above
- Risk of stroke in the presence of atrial fibrillation predominantly depends on the risk of stroke due to atrial fibrillation, though may be somewhat higher in some situations. Cases must be evaluated on basis of presence of additional risk factors (for example, CHADS2 or CHA2DS2-VASc criteria, and understanding that they have been quantified only for nonvalvular atrial fibrillation) and prevailing clinical circumstances.

CHADS2 Risk Factors and Score (note that the BRIDGE study used this scoring system; current determinations are based on CHA$_2$DS$_2$-VASc, noted below[86]:

CHADS2 Stroke Risk Factors	Score
Congestive heart failure	+1
Hypertension	+1
Age 75 years or older	+1
Diabetes mellitus	+1
History of stroke or TIA[87]	+2

Score	Yearly risk of stroke untreated	Risk of a Stroke
0	• Low risk of thromboembolic event. 1.9% risk of event per year if no warfarin	Low
1	• Intermediate risk of thromboembolic event. 2.8% risk of event per year if no warfarin	Moderate
2	• Intermediate risk of thromboembolic event. 4.0% risk of event per year if no warfarin	High
3	• High risk of thromboembolic event. 5.9%risk of event per year if no warfarin	High
4	• High risk of thromboembolic event. 8.5% risk of event per year if no warfarin	High
5	• Note: While history of stroke provides 2 points, most physicians would move these patients directly to the high risk group (>8.5% risk of event per year if no warfarin) • By points directly: High risk of thromboembolic event. 12.5% risk of event per year if no warfarin.	High
6	• Note: While history of stroke provides 2 points, most physicians would move these patients directly to the high risk group (>8.5% risk of event per year if no warfarin) • By points directly: High risk of thromboembolic event. 18.2% risk of event per year if no warfarin	High

CHA$_2$DS$_2$-VASc Risk Factors and Score:

For patients with AF, including those with paroxysmal AF, stroke risk should be assessed using a risk factor based approach, rather than a categorization into low, moderate/high risk strata. We recommend use of the CHA2DS2-VASc as a simple clinically-based stroke risk score to initially identify “low stroke risk” patients who should not be offered antithrombotic therapy to prevent stroke and reduce mortality. We have applied the *CHA$_2$DS$_2$-VASc* score to the previous risk table, as noted above.

[86] CHADS2 study figures from Gage BF, Waterman AD, Shannon W, et al: Validation of Clinical Classification Schemes for Predicting Stroke: Results from the National Registry of Atrial Fibrillation. Journal of the American Medical Association 2001; 285: 2564-2870

[87] Patients with history of documented atrial clots may be considered at similar risk as those with history of TIAs or strokes. This recommendation is not based on referenced CHADS2 or CHA2DS2-VASc criteria, but is logical since cardioembolic strokes presumably arise from these atrial clots. It is relevant for a reasonable amount of time (e.g., one year) after discovery of the atrial clot in self-limited circumstances (e.g. occurring after cardiac surgery or an MI), or indefinitely when the reason for the previously documented atrial clot has not resolved (e.g. chronic atrial fibrillation with large left atrium).

CHA2DS2-VASc Stroke Risk Factors	Score
Congestive heart failure	+1
Hypertension	+1
Age 65-74	+1
Age 75 years or older	+2
Diabetes mellitus	+1
History of stroke or TIA	+2
Female gender	+1
Cardiovascular disease (defined as PVD, prior MI, or aortic plaque)	+1

Thrombotic risk by CHA2DS2-VASc:

CHA2DS2-VASc Score	Yearly Risk of stroke untreated	Yearly risk of stroke/TIA/Systemic embolism untreated	Risk for females	Risk for males
0	0.2%	0.3%	low	low
1	0.6%	0.9%	low	moderate
2	2.2%	2.9%	high	high
3	3.2%	4.6%	high	high
4	4.8%	6.7%	high	high
5	7.2%	10.0%	high	high
6	9.7%	13.6%	high	high
7	11.2%	15.7%	high	high
8	10.8%	15.2%	high	high
9	12.2%	17.4%	high	high

Stroke risk documented in Swedish Atrial Fibfrillation Cohort[88]

[88] Friberg et al; Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study; European Heart Journal (2012) 33, 1500–1510

Appendix 7: General Recommendations for Perioperative Anticoagulation[89] (see also: Perioperative Management of Direct Oral Anticoagulants (DOACs) and Antiplatelet Therapy (Atrius P&T)

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation:

j.jacc.2016.11.024.full.pdf

Common Procedures and Associated Procedural Bleed Risk:

PMAC_Online_Appendix.pdf

Principles of management

- **For patients on warfarin**
  1. Most patients who require a hold of warfarin for surgery should begin holding warfarin ~5 days before surgery. Patients managed at target ranges above 2.0-3.0 (or with recently higher values) and patients undergoing procedures with very high risk of bleeding (e.g. spinal surgery) may require a 7-day hold.
  2. Patients holding warfarin should restart warfarin 12 to 24 hours after surgery, assuming there is adequate hemostasis.
  3. Use of bridging parenteral heparin (usually LMWH) should be considered in the following scenarios
     - patients with high risk mechanical valves, or mechanical valves in the presence of atrial fibrillation
     - warfarin-treated patients at high risk of stroke or systemic embolism, including those with a CHA_2DS_2-VASc score of 7-9 or a recent (within 3 months) ischemic stroke, or warfarin-treated patients with a prior stroke or systemic embolism (≥3 months previously) who are not at a significant periprocedural bleeding risk. In this last case, bear in mind that the risk related to a stroke dissipates over time, so the benefit of bridging becomes less compelling. These cases always require review with a consultant.
  4. Patients with mechanical heart valves or VTE should receive perioperative management with or without bridging based on stratification of high or low risk, respectively, of thromboembolism.
     - Patients with mechanical heart valves or VTE at low risk of thromboembolism should not be bridged with LMWH when warfarin is held.
     - Patients with mechanical heart valves or VTE at high risk of thromboembolism should be bridged with LMWH when warfarin is held.

[89] Recommendations are based on Gould, M et al. Prevention of VTE in Nonorthopedic Surgical Patients and Douketis, J et al. Perioperative Management of Antithrombotic Therapy, both in Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Individual treatment decisions should be based on risk of bleeding vs. thrombolembolism in individual patients.

- Patients with mechanical heart valves or VTE at moderate risk of thromboembolism require a clinical decision based on the clotting risk, nature of surgery, and values of the patient regarding the prevention of thromboembolism vs. postoperative bleeding and the costs and inconvenience of bridging.

5. Perioperative management without use of bridging should follow the following standardized protocol for holding and resuming warfarin, as noted above. Typically, warfarin is restarted on the evening after or day after the procedure at the patient's usual dose, assuming hemostasis has been obtained and resumption has been approved by the specialist performing the procedure.
6. In most situations, patients receiving aspirin for secondary prevention of cardiovascular disease should continue rather than hold aspirin for 7-10 days prior to the procedure. Patients taking aspirin for primary prevention of cardiovascular disease should hold aspirin for 7-10 days.
7. Patients taking dual antiplatelet therapy for secondary prevention, for example, in the presence of coronary artery stents, should consult with their cardiologists to determine the appropriate perioperative antiplatelet management plan.
8. Patients receiving therapeutic LMWH for bridging should receive the last dose approximately 24 hours before the procedure; this last dose should be no more than half the usual daily therapeutic dose or, when relevant, dose adjusted for reduced renal function. Patients receiving prophylactic LMWH for bridging may receive the full prophylactic dose 24 approximately 24 hours before the procedure.
9. Patients receiving therapeutic LMWH for bridging should resume LMWH approximately 24 hours after low and moderate bleeding risk procedures, and 48 to 72 hours after high bleeding risk procedures, after clearance by the physician performing the procedure.

Does procedure require holding warfarin? If so, how long is the hold?

1. **For Low bleed risk procedures** (most dental procedures, most cataract operations, and minor dermatologic procedures, warfarin can be continued at therapeutic range before, during, and after the procedure.
   - **Dental procedures:** Most patients are not at high risk for serious bleeding from dental procedures. Accordingly, CHEST guidelines currently suggest continuing anticoagulation or stopping vitamin K antagonists two to three days before the procedure, using local measures to control bleeding (pressure or 5% aminocaproic acid mouthwash, generally prescribed by dentist). For high bleeding risk procedures, a longer hold may be considered. For specific procedure recommendations, consult the following site: https://depts.washington.edu/anticoag/home/content/suggestions-anticoagulation-management-and-after-dental-procedures (University of Washington Medical Center Anticoagulation Clinic).
   - **Cataract operations:** For uncomplicated cataract surgery (i.e. not including complicated cataract surgery, such as concurrent glaucoma surgery), warfarin should generally not be stopped. However, all patients on anticoagulation who do not hold warfarin the last 4 days before surgery will have an INR drawn at MEEI prior to the procedure, and patients with an INR of above 3.0 may be cancelled. Therefore, we are requesting that all anticoagulation patients have an INR drawn within 7 days of surgery, with appropriate adjustments in management to insure that the INR will be will be ≤3.0 at the time of the procedure. In some circumstances, this may require a temporarily dose adjustment or a one to two day hold, and in rare circumstances, use of small doses of vitamin K (such as over the counter vitamin K 100 mcg – up to 5 tablets). If the patient was previously in therapeutic range, regardless of the intervention, he/she should return to prior dosing after the procedure. If patient is having more extensive or complicated cataract surgery, including glaucoma surgery, follow directions below for moderate bleed risk procedure. For specific Atrius Health ophthalmology parameters, refer to Eye Surgery Anticoagulation Parameters (HVMA).
   - **Minor dermatologic procedures**: Warfarin should not be stopped for skin biopsies and all minor dermatologic procedures where bleeding can be reasonably controlled by local measures.
2. For most patients who are therapeutic in the range 2.0-3.0, it takes approximately 5 days (corresponding to 5 half-lives of warfarin) to reach an INR of 1.5 or less (the usual goal the day before most procedures) and 7 days (corresponding to 7 half-lives of warfarin) to reach an INR of 1.2 or less (the goal the day before high risk procedures). **For procedures not clearly falling into moderate or high risk, it is essential to check with the surgeon to clarify the INR range desired prior to surgery, since the determination of the duration of hold cannot be done without a clear understanding of the goal.**

3. **For moderate to high risk bleed risk procedures that require an INR of 1.5 or less on the day prior to surgery**: **hold warfarin for 5 days before the procedure** (when INR >3.0, warfarin may need to be held for 6-7 days before surgery). If INR is above 1.5 on day prior to surgery, and surgery cannot be postponed, consider either ¼ of vitamin K (Mephyton) 5.0mg oral tablet (approximately 1.25 mg) or ten vitamin K1 100mcg over-the-counter tablets (approximately 1.0mg - widely available at Atrius Health and other local pharmacies). Unless INR is extremely close to 1.5 before administration of vitamin K, INR should be repeated before surgery.
4. As above, most patients with atrial fibrillation with CHA2DS2-VASc scores ≤4 without stroke or other embolic event will not need bridging in the above situations. Patients with mechanical valves and VTE should be bridged according to usual thromboembolic and bleeding risk assessment.
5. **For epidural injections, which require an INR of 1.3 or less on the day prior to surgery: hold warfarin for 5-7 days before the procedure.** This desired goal range has been reviewed with Atrius Pain Management, BWH Pain Management, and North Shore Pain Management. Though various guidelines provide conflicting information, this plan will provides a conservative approach that is similar to all available guidelines.
6. **For very high bleed risk procedures that require an INR of 1.2 or less on the day prior to surgery** (e.g. spinal surgery not including epidural injections, some urologic, orthopedic, and cardiac procedures), **hold warfarin for 7 days before the procedure.** If INR is above 1.2, consider either ¼ of vitamin K 5.0mg oral tablet (Mephyton 5mg) or ten vitamin K1 100mcg tablets (over-the-counter). INR should be repeated before the procedure.

For a list of common procedures and associated procedural bleeding risk, please refer to the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation: Online Appendix. *Note that the complexity of any given procedure may vary, so the decision of bleeding risk must adhere to the opinion of the clinician performing the procedure, which may vary from the guidelines of this document.*

Risk Assessment for GI Procedures

Procedure bleeding risk	**Condition risk for Thromboembolism**	
	High	**Low**
High	Discontinue warfarin ~5 days before procedure, based on most recent INR. Bridge with LMWH while INR is below therapeutic level. Reinstate warfarin 12-24 after procedure. Resume LMWH after clearance by gastroenterologist.	Discontinue warfarin ~5 days before procedure, based on most recent INR. Reinstate warfarin 12-24 after procedure
Low	No change in anticoagulation. Elective procedures should be delayed while INR is in supratherapeutic range.	
Procedure risk		
High-risk procedures	**Low risk procedures**	
• Polypectomy • Sphincterotomy, biliary or pancreatic • Pneumatic or bougie dilation • PEG (percutaneous endoscopic gastrostomy) placement • Therapeutic balloon-assisted enteroscopy EUS (endoscopic ultrasound) with fine needle aspiration (FNA)	• Diagnostic 1. EGD ± biopsy 2. Flex sig ± biopsy 3. Colonoscopy ± biopsy • ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy • Push enteroscopy and diagnostic balloon-assisted	

• Endoscopic hemostasis • Tumor ablation • Cystogastrostomy • Ampullary resection • EMR (endoscopic mucosal resection) • Endoscopic submucosal dissection • PEJ (percutaneous endoscopic jejunostomy) • Treatment of varices	enteroscopy • Capsule endoscopy • Enteral stent deployment (controversial) • EUS (endoscopic ultrasound) without fine needle aspiration (FNA) • Argon plasma coagulation • Barrett's ablation

Modified from American Society of Gastrointestinal Endoscopy (ASGE): Guideline on The management of antithrombotic agents for patients undergoing GI endoscopy; volume 83, number 1, 2016.

GI procedures at Atrius Health Endoscopy Unit:

Atrius GI
Anticoagulation Gri

Does procedure require holding a DOAC? If so, how long is the hold?

Classification of Elective Surgical Interventions According to Bleeding Risk		
Interventions Not Necessarily Requiring Discontinuation of Anticoagulation	**Minor Bleeding risk (i.e., infrequent or with low clinical impact)**	**Major Bleeding Risk (i.e., frequent and/or with high impact)**

▪ Dental interventions
  ○ Extraction of 1 to 3 teeth
  ○ Periodontal surgery
  ○ Incision of abscess
  ○ Implant positioning
▪ Cataract or glaucoma intervention
▪ Superficial surgery (e.g., abscess incision, small dermatologic excisions)
▪ Thyroid nodule or neck lymph node fine needle aspiration biopsy
	▪ Prostate or bladder biopsy
	▪ Electrophysiological study or catheter ablation (except complex procedures)
	▪ Non-coronary angiography
	▪ Pacemaker or ICD implantation (unless complex anatomical setting, e.g., congenital heart disease)
		▪ Spinal or epidural anesthesia; lumbar diagnostic puncture
		▪ Thoracic surgery
		▪ Abdominal surgery
		▪ Major orthopedic surgery
		▪ Liver or kidney biopsy
		▪ Transurethral prostate resection
		▪ Extracorporeal shockwave lithotripsy
		▪ Complex left-sided ablation (pulmonary vein isolation; some VT ablations)

Classification of GI procedures According to Bleeding Risk[90]	
Low risk procedures (Minor Bleeding Risk)	**High-risk procedures (Major Bleeding Risk)**

• Diagnostic
  ○ EGD ± biopsy
  ○ Flex sig ± biopsy
  ○ Colonoscopy ± biopsy
• ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
• Push enteroscopy and diagnostic balloon-assisted enteroscopy
• Capsule endoscopy
• Enteral stent deployment (controversial)
• EUS (endoscopic ultrasound) without fine needle aspiration (FNA)
• Argon plasma coagulation
• Barrett's ablation
	• Polypectomy
	• Sphincterotomy, biliary or pancreatic
	• Pneumatic or bougie dilation
	• PEG (percutaneous endoscopic gastrostomy) placement
	• Therapeutic balloon-assisted enteroscopy EUS (endoscopic ultrasound) with fine needle aspiration (FNA)
	• Endoscopic hemostasis
	• Tumor ablation
	• Cystogastrostomy
	• Ampullary resection
	• EMR (endoscopic mucosal resection)
	• Endoscopic submucosal dissection
	• PEJ (percutaneous endoscopic jejunostomy)
	• Treatment of varices

For patients on a DOAC

- For patients on DOAC therapy who require interruption of anticoagulation therapy pre-procedurally, the number of doses to be held is determined by the estimated creatinine clearance and the procedural bleeding risk. See procedures that require DOAC interruption table above.
- DOAC therapy should not be used in patients undergoing mechanical valve replacement.[91]
- Decisions regarding DOAC interruption require consideration of **thromboembolic risk vs. bleeding risk** and should involve discussion between the primary prescriber of the anticoagulant and the proceduralist.
- Confer with individual proceduralists to determine if anticoagulation interruption is required prior to any surgery/procedure.
- DOACs generally do not need to be stopped prior to a minor dental procedure, cataract surgery, or minor dermatologic surgery.
- When DOAC interruption is indicated, recommendations regarding perioperative management should consider individual renal function and procedural bleeding risk.
- **Bridging therapy is NOT recommended for most patients on DOACs** due to their rapid offset and onset of action.
- Post-operatively, only restart DOACs once adequate hemostasis has been achieved and maintained

Pre-operative Management of DOACs:

[90] Adapted from Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the Use Of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Eur Heart J. 2018;39(16):1330-1393

[91] ACC Consensus Pathway for Perioperative Management of non-valvular AF - 2017

- Usually hold DOACs for 2-3 half-lives prior to minor-risk procedures and 4-5 half-lives prior to major-risk procedures (see chart below).
- In patients taking concomitant dronedarone, amiodarone or verapamil, an extra 24 hours of interruption can be considered, especially if thromboembolic risk is not very high (CHA_2DS_2-VASc ≤3) (*Steffel J. et al, Eur Heart J. 2018*).
- **For patients with severe renal dysfunction (CrCl <30 mL/min) who are generally ineligible for DOACs but taking them, perioperative management is less clear.** Apixaban, rivaroxaban, and edoxaban may require at least an additional day of interruption prior to procedures. Dabigatran should be stopped at least 5 days (held 120 hours) before a major bleeding risk procedure and at least 3 days (held 72 hours) before a minor bleeding risk procedure.
- **For procedures that require DOAC interruption, refer to the table below for general instructions on DOAC interruption based on creatinine clearance and surgical bleeding risk:**

Pre-operative Interruption of DOACs Before Minor Bleeding Risk and Major Bleeding Risk Procedures*			
DOAC	**Creatinine Clearance (CrCl)**** (Based on Cockcroft-Gault)	**Minor Bleeding Risk Procedure**	**Major Bleeding Risk Procedure**
apixaban (Eliquis)	**CrCl >30mL/min** *($t_{1/2}$ ~12 hrs)*	**Skip 2 doses - holding 24 hours** Last dose taken 2 days before surgery	**Skip 4 doses - holding 48 hours** Last dose taken 3 days before surgery
rivaroxaban (Xarelto)	**CrCl >30mL/min** *($t_{1/2}$ ~5-13 hrs)*	**Skip 1 dose - holding 24 hours** Last dose taken 2 days before surgery	**Skip 2 doses - holding 48 hours** Last dose 3 days before surgery
dabigatran (Pradaxa)	**CrCl ≥80mL/min** *($t_{1/2}$ ~12-14 hrs)*	**Skip 2 doses - holding 24 hours** Last dose taken 2 days before surgery	**Skip 4 doses - holding 48 hours** Last dose taken 3 days before surgery
	CrCl 50-79mL/min *($t_{1/2}$ ~17 hrs)*	**Skip 3 doses - holding 36 hours** Last dose taken AM 2 days before surgery	**Skip 6 doses - holding 72 hours** Last dose taken 4 days before surgery
	CrCl 30-49 mL/min *($t_{1/2}$ ~19 hrs)*	**Skip 4 doses - holding 48 hours** Last dose taken 3 days before surgery	**Skip 8 doses - holding 96 hours** Last dose taken 5 days before surgery
edoxaban++ (Savaysa)	**CrCl >30mL/min** *($t_{1/2}$ ~10-14 hrs)*	**Skip 1 dose - holding 24 hours** Last dose taken 2 days before surgery	**Skip 2 doses - holding 48 hours** Last dose taken 3 days before surgery

** Recommendations are based on published expert opinion and may differ or be more specific than FDA package insert labeling.*
*** Xarelto, Pradaxa, and Savaysa clinical trials used actual body weight to calculate CrCl, while Eliquis trials did not specify. Clinical judgment should be used when calculating CrCl in overweight/obese patients. Using actual body weight may overestimate renal function in this population; therefore use of an adjusted body weight in these patients may be a more practical approach.* ***Use ".CreatCl" SmartLink in Epic to estimate CrCl*** *(per Cockcroft-Gault) according to various body weights, depending on patient BMI. This calculator can also be used.*
++ Avoid edoxaban in patients with CrCL> 95 mL/min for stroke prevention in NVAF due to increased risk of ischemic stroke compared to warfarin

Post-operative Management of DOACs:

- **DOACs should only be restarted once adequate hemostasis has been achieved and maintained, as peak anticoagulant effect will occur within a few hours after initiation.**
- For procedures with associated immobilization, it may be appropriate to initiate a prophylactic-dose LMWH (e.g., enoxaparin 30 mg SQ twice daily or 40 mg SQ once daily, dalteparin 5000 units SQ once daily) 6 to 8 hours after surgery if hemostasis has been achieved until DOACs can be resumed.
- For patients with AF at high risk for thromboembolism undergoing a high risk procedure, some experts suggest administering a reduced dose of the DOAC (e.g., dabigatran 75mg twice daily, rivaroxaban 10mg daily, apixaban 2.5mg daily) on the evening after surgery and on the following day after surgery. However, there are no safety and efficacy data available to support this approach.

Risk of Procedure	Resumption of DOAC
Procedures with immediate and complete hemostasis	6 to 8 hours post-op if approved by surgeon
Minor bleeding risk procedure	24 hours post-op if approved by surgeon
Major bleeding risk procedure	48 to 72 hours post-op if approved by surgeon

See 2017 ACC Online Appendix (Common Procedures and Associated Procedural Bleed Risk).

RESUMPTION OF DOACS AFTER A MAJOR BLEED:

The decision to resume anticoagulation following a major bleeding event should be made based on numerous factors, including the location of bleed, factors contributing to the bleed, comorbid conditions, thromboembolic risk, and patient/family preferences. Available evidence suggests that in most cases, resumption of anticoagulation results in better patient outcomes. The following table can be used to help decide if anticoagulation should be resumed.

Clinical characteristics arguing for or against resuming anticoagulation after major bleed

	Resume	Do not resume
Bleed-related characteristics		
-Known correctable source	consider very strongly	
-Known, uncorrectable source	consider	
-Unknown source		consider
-Nonlobar ICH location	consider, particularly if strong indication for anticoagulation	
-Lobar ICH location		consider strongly, given relatively high risk of ICH recurrence
Indication for anticoagulation		
-Mechanical heart valve	consider very strongly	
-Idiopathic or recurrent VTE	consider very strongly	
-Provoked VTE, completed 3 months of therapy		consider very strongly
-VTE +protein C/S or antithrombin deficiency or APLA syndrome	consider strongly	
-AF and prior history of stroke or higher CHADs2Vasc score	consider very strongly	
-AF and lower CHADs2Vasc score	consider	
-AF and no additional stroke risk factor		consider very strongly

Other characteristics		
-Previously unstable INR control despite adequate adherence		consider
-Renal failure		consider
-Poor prognosis, limited life expectancy		consider

- Other important factors include: concurrent use of antiplatelets or NSAIDs, INR at time of bleed, and other comorbid conditions that increase risk of bleed (e.g. Liver disease, hypertension, alcohol abuse).
- Age alone should not be a reason to withhold anticoagulation after a bleeding event.
- Although evidence related to anticoagulation resumption following major bleeding events is based on gastrointestinal and intracranial bleeds in patients taking warfarin, it is reasonable to extrapolate to other types of bleeds and to patients taking DOAC's.

When to resume anticoagulation after a Major Bleed:

Bleed location	**When to resume**
Gastrointestinal	Approximately 14 days
Intracranial	At least 4 weeks, and requiring approval resumption of anticoagulation by neurosurgeon or neurologist caring for patient
Other	Once bleeding is resolved and hemostasis is normalized, consider restarting the anticoagulant after weighing risks and benefits of therapy vs no therapy

Adapted from: Anticoagulation Toolkit v1.9 (Michigan Quality Improvement Initiative/BCBS of Michigan) (page 49)
See also: 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants

Note: when resumption is appropriate, the lack of resumption beyond four weeks is highly associated with recurrent thromboembolic events.

LINKS TO ADDITIONAL RESOURCES:

- Thrombosis Canada Resources
- Anticoagulation Forum Resource Center
- European Heart Rhythm Association Practical Guide on DOACs in NVAF
- North American Thrombosis Forum
- UW Anticoagulation Services

Managing Nuisance Bleeding:

- Living Your Best Life While Taking Blood Thinners: Don't Let Nuisance Bleeding Worry You
- Taking Care of Nosebleeds
- Taking Care of a Cut

- Blood in Stool, Urine, or Vagina
- Taking Care of Bruises

2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation:

j.jacc.2016.11.024.full.pdf

2017 ACC Online Appendix (Common Procedures and Associated Procedural Bleed Risk):

PMAC_Online_Appendix.pdf

Does patient require a "bridge" when warfarin is held prior to a procedure?

Suggested Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism			
	Indication for warfarin Therapy		
Short-Term Thrombotic Risk	**Mechanical Heart Valve**	**Atrial Fibrillation**	**VTE**
High*	• Any mitral valve prosthesis • Older (caged-ball or tilting disc) aortic valve prosthesis • Recent (within 6 months) stroke or transient ischemic attack	• CHA2DS2-VASc score ≥7 • Recent (within 3 months) stroke, transient ischemic attack or systemic embolism • Rheumatic valvular heart disease	• Recent (within 3 months) VTE • Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, or multiple abnormalities)
Moderate	• Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age ≥75yr	• CHA2DS2-VASc score of 5 or 6 • History of (≥ 3 months previously) stroke, transient ischemic attack, or systemic embolism	• VTE within the past 3 to 12 months • Non-severe thrombophilic conditions (e.g. heterozygous Factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 months or palliative)
Low	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• CHA2DS2-VASc ≤4 (and no prior stroke, transient ischemic attack, or systemic embolism)	• Single VTE occurred >12 months ago and no other risk factors

*High-risk patients may also include those with prior thromboembolism during temporary interruption of warfarin, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (e.g., cardiac valve replacement, carotid endarterectomy, major vascular surgery).

Classification: High (>10% annual risk for thromboembolism); Moderate: (5-10% annual risk for thromboembolism); Low (<5% annual risk for thromboembolism)

Above table modified from: The Perioperative Management of Antithrombotic Therapy; CHEST/141/2/February, 2012 Supplement; page 330S and the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation (PDF of document above).

Considerations regarding bridging:

1. Decisions regarding bridging depend on the thrombotic risk of the patient, the expected duration of subtherapeutic values, and the reason for interruption of anticoagulation. In addition, the presence or absence of other agents that may affect clotting (such as antiplatelet agents) may affect this consideration.
2. Patients at **high or very high thrombotic risk** require bridging in almost all situations requiring interruption of anticoagulation, regardless of duration of the interruption or cause of the interruption, with possible exception to patients who have had a major bleed or intracranial hemorrage within the last 3 months. Bridging should be with therapeutic-dose LMWH. This principle applies to surgery and other procedures requiring holding anticoagulation, as well as unanticipated significantly subtherapeutic values in high risk patients, including one or more of the following scenarios:
   - INR more than 0.5 below target range, regardless of stability of patient,
   - INR below 1.8 as a repeat of a prior test that was also below therapeutic range
3. Patients at **moderate thrombotic risk**:
   - Patients with mechanical heart valves or VTE require a clinical decision based on the clotting risk, nature of surgery, and values of the patient regarding the prevention of thromboembolism vs. postoperative bleeding and the costs and inconvenience of bridging. Bridging is required when interruption of anticoagulation will be prolonged or for a procedure that may be expected to significantly increase the patient's thrombotic risk, such as extensive surgery and/or anticipated post-operative immobilization or bedrest. These factors, though most relevant to the risk of venous thromboembolism, may also increase the likelihood of arterial clots by initiation of the clotting cascade, hence causing a relatively prothrombotic environment. In addition, the elimination of anti-platelet agents, frequently done at the time of surgery, may also increase the likelihood of clotting.
   - Patients with nonvalvular atrial fibrillation:
     - If patient is at increased risk of bleeding (major bleed or intracranial hemorrhage in previous 3 months, quantitative or qualitative platelet abnormality including aspirin use, INR above therapeutic range, or prior bleed from previous bridging), interruption of warfarin without bridging generally recommended.
     - If patient has no significant bleed risk with no prior stroke, TIA, or systemic embolism, interruption of warfarin without bridging generally recommended.
     - If patient has no significant bleed risk and has had prior stroke, TIA, or systemic embolism, bridging should be considered.
   - Bridging should be with therapeutic-dose LMWH, although low dose LMWH may be acceptable under some circumstances, such as an anticipated short period of interruption of warfarin therapy, the continued co-prescription of antiplatelet agents, and the presence of factors increasing the bleeding risk of the patient, including existing patient co-morbidities and the bleeding risk of the planned surgery Therefore, these patients require consideration on a case by case basis in consultation with a consultant, who may defer the decision to the PCP, appropriate specialist, or surgeon, as indicated by the circumstances of the case.
4. Patients at **low thrombotic risk** do not require bridging for interruption of anticoagulation for surgery, procedures, or other subtherapeutic occurrences. In some situations, post-operative immobilization may still require prophylactic dose LMWH after surgery.
5. Patients receiving bridging with therapeutic dose LMWH should receive their last dose of LMWH approximately 24 hours before the procedure. They should receive only the morning dose if on a twice daily dosing schedule and only 50% of the total daily dose if on a once daily schedule.
6. Patients receiving prophylactic dose regimens who do not have reasons for low dosing such as renal failure may receive their full prophylactic dose up to 24 hours before the procedure.

When can anticoagulation restart?

1. Timing of restart of warfarin and LMWH/Fondaparinux must occur in coordination with the responsible surgeon or other specialist, based on post procedure bleeding risk and actual bleeding.
2. Restart warfarin 12 to 24 hours after surgery and when there is adequate hemostasis. When procedure has been completed early in the day, warfarin usually can be restarted the evening of the day of the procedure. Consider loading with three times the usual daily dose for first two days, then decreasing to usual dose. Check INR 3-5 days after warfarin restart. Note that up to three times the usual dose on the first day will accomplish the same objective about one day more rapidly. However, would not use that approach unless the procedure included no risk of bleeding (such as a colonoscopy or upper endoscopy with no biopsy).
3. In general, patients undergoing a minor surgical or other invasive procedure (low and some moderate risk procedures above), who have been bridged before the procedure, may resume the bridging regimen 24 hours after the procedure when there is adequate hemostasis.
4. Patients undergoing a major surgical or invasive procedure with high risk of bleeding, who have been bridged before the procedure, may resume bridging by one of the following options, in consultation with the responsible surgeon or other specialist:
   - Delay resumption of therapeutic dose LMWH for 48-72 hours after surgery, when hemostasis is secured and cleared by the surgeon.
   - Begin low dose prophylactic LMWH 24 hours after the procedure once hemostasis is secured, and resume therapeutic dose LMWH 48-72 hours after surgery.
5. The AMS manager will discontinue LMWH, if prescribed, once INR reaches therapeutic range.
6. Note: Anticoagulation managers will provide verbal and written instructions to all patients requiring a hold of warfarin for a procedure, and fax or electronically send a copy of the instructions to the physician performing the procedure.

Management of Patients Requiring LMWH:

Preoperative management to reach goal of INR of 1.5 or less on day prior to procedure:

- Day (- 5): Stop warfarin. (Note: in patients with INR >3.0, warfarin may need to be held for 6-7 days prior to procedure.)
- Day (-3): Start LMWH (full or prophylactic dose depending on thromboembolic risk) in AM. LMWH is started 36 hours after stopping warfarin (assuming evening dose of warfarin and first dose of LMWH in AM).
- Day (-1): Discontinue LMWH 24+ hours prior to procedure. If twice daily schedule, take usual dose the morning of the day before surgery. If once daily dose and on treatment dose LMWH, reduce it by 50% and take the morning of the day before surgery. If on prophylactic daily dose, may take entire dose in morning of the day before surgery.
- Day (-1): Check INR (goal ≤1.5). If INR is >1.5, ten 100mcg vitamin K1 tablets (over-the-counter) or Vitamin K 1.25mg (1/4 of 5mg pill) should be considered. If INR is 1.6 - 1.7 and is decreasing, Vitamin K is generally not needed; however, INR should be checked stat on morning of surgery to make sure it is within acceptable range.
- Day (0): Procedure day.

Preoperative management for procedures that require INR of 1.3 or less on day prior to procedure (e.g. epidural injections):

- Day (-5-to -7, depending on baseline INR): Stop warfarin.
- Day (-3 to -5): Start LMWH. LMWH is started 36 hours after stopping warfarin (assuming evening dose of warfarin and first dose of LMWH in AM).

- Day (-2): Stop LMWH 48 hours prior to procedure for patients undergoing neurosurgery only.
- Day (-1): Discontinue LMWH 24+ hours prior to procedure. If twice daily schedule, take usual dose the morning of the day before surgery. If once daily dose and on treatment dose LMWH, reduce it by 50% and take the morning of the day before surgery. If on prophylactic daily dose, may take entire dose in morning of the day before surgery.
- Day (-1): Check INR (goal ≤1.3). If INR is >1.3, ten 100mcg vitamin K1 tablets (over-the-counter) or Vitamin K 1.25mg (1/4 of 5mg pill) should be considered
- Day (0): Procedure day.

Postoperative management:

- Day (0) or Day (+1): Restart warfarin 12-24 hours after procedure, after hemostasis has been secured.
- **In all cases, timing of resumption of LMWH should be cleared by surgeon or other managing clinician (e.g. anesthesiologist or pain management physician administering ESI) responsible for the procedure.** Options include starting LMWH at therapeutic dose 24 hours after surgery once hemostasis has been secured (low to moderate bleeding risk surgery), deferring start of bridging LMWH for 48-72 hours at therapeutic dose or starting prophylactic dose LMWH 24 hours after surgery once hemostasis has been secured, then changing to therapeutic dose LMWH 48-72 hours after surgery once hemostasis has been secured, or in some selected cases, starting prophylactic dose LMWH 24 hours after surgery once hemostasis has been secured, and increasing to full therapeutic dose 48-72 hours after surgery.
- Restart warfarin 12 to 24 hours after surgery and when there is adequate hemostasis. Consider loading with three times the usual daily dose for one day, then decreasing to usual dose and checking INR 3-4 days after warfarin restart. Continue to monitor INRs every one to two days until INR is in therapeutic range. LMWH may be discontinued when INR reaches therapeutic range.

Preoperative management for procedures that require INR of 1.2 or less on day prior to procedure (e.g. spinal surgery, not including epidural injections:

- Day (-7): Stop warfarin (may stop on Day -5 for low INRs).
- Day (-5): Start LMWH. LMWH is started 36 hours after stopping warfarin (assuming evening dose of warfarin and first dose of LMWH in AM).
- Day (-2): Stop LMWH 48 hours prior to procedure for patients undergoing neurosurgery only.
- Day (-1): Discontinue LMWH 24+ hours prior to procedure. If twice daily schedule, take usual dose the morning of the day before surgery. If once daily dose and on treatment dose LMWH, reduce it by 50% and take the morning of the day before surgery. If on prophylactic daily dose, may take entire dose in morning of the day before surgery.
- Day (-1): Check INR (goal ≤1.2). If INR is >1.2, ten 100mcg vitamin K1 tablets (over-the-counter) or Vitamin K 1.25mg (1/4 of 5mg pill) should be considered
- Day (0): Procedure day.

Postoperative management:

- Day (0) or Day (+1): Restart warfarin 12-24 hours after procedure, after hemostasis has been secured.
- **In all cases, timing of resumption of LMWH should be cleared by surgeon or other clinician (e.g. cardiologist implanting pacemaker or AICD or gastroenterologist performing colonoscopy) responsible for the procedure.** Options include starting LMWH at therapeutic dose 24 hours after surgery once hemostasis has been secured (low to moderate bleeding risk surgery), deferring start of bridging LMWH for 48-72 hours at

therapeutic dose or starting prophylactic dose LMWH 24 hours after surgery once hemostasis has been secured, then changing to therapeutic dose LMWH 48-72 hours after surgery once hemostasis has been secured, or in some selected cases, starting prophylactic dose LMWH 24 hours after surgery once hemostasis has been secured, and increasing to full therapeutic dose 48-72 hours after surgery.

- Restart warfarin 12 to 24 hours after surgery and when there is adequate hemostasis. Consider loading with twice usual daily dose for first two days, then checking INR 3-4 days after warfarin restart. Continue to monitor INRs every one to two days until INR is in therapeutic range. LMWH may be discontinued when INR reaches therapeutic range.

Appendix 8: ANTICOAGULATION MGT. FOR PATIENTS HAVING ORTHOPEDIC SURGERY

- Based on the 2019 ASH guideline on prevention of VTE in surgical hospitalized patients[92], aspirin or anticoagulants are recommended options for VTE prophylaxis in patients undergoing total hip arthroplasty or total knee arthroplasty. When anticoagulants are used, DOACs are suggested over low-molecular-weight heparin (LMWH), basing choice of DOAC on insurance formulary coverage and approved indications. If not feasible to use DOACs or LMWH and anticoagulation is desired, warfarin can be considered. Unfractionated heparin is not recommended. **Error! Bookmark not defined.**

Anticoagulation Options for Orthopedic Surgery with Risk of Post-Procedure VTE:

Procedure	Options for anticoagulation	Comments
Elective THR and TKA and hip fracture surgery	**Option 1:** Aspirin ~160mg daily, when anticoagulation not used **Option 2:** Apixaban (Eliquis) - 2.5mg orally twice daily started 12 to 24 hours after closure of the surgical wound; **Option 3:** Dabigatran (Pradaxa) – 150mg once daily, starting with a half-dose 1-4 h after surgery **Option 4:** Rivaroxaban (Xarelto) – 10mg daily at least 6-10 hours after surgery once hemostasis has been established **Option 5:** LMWH– started 12+ hours before surgery or 12+ hours after surgery at full prophylactic dose [enoxaparin (Lovenox) 30mg bid or 40mg qd if twice daily dosing not feasible]. **Option 6:** Fondaparinux (Arixtra) 2.5mg/day started 6-8 hours after surgery **Option 7:** Warfarin started before surgery or on the evening after surgery with INR target of 2.5, range of 2-3 or INR target of 2.0, range of 1.8-2.3 per orthopedist's recommendation)[94]	• Anticoagulation should be continued for at least 10-14 days, and suggested up to 35 days (5 weeks), based on patient's thrombotic risk, as determined by the treating orthopedist. • It is preferable to use dual therapies to include at least an IPCD while in the hospital plus any of the noted drug options. • *Low-dose aspirin given before major orthopedic surgery and continued for 35 days will result in seven fewer symptomatic VTEs per 1,000 but at the expense of a possible 3 more major bleeding episodes and 2 additional nonfatal myocardial infarctions per 1,000, thus resulting in a close balance between desirable and undesirable effect.*[93] • Although not in CHEST guidelines, it is reasonable to consider treating first with LMWH followed by dose-adjusted warfarin or aspirin.
Elective THR and TKR, and HFS (with increased risk of bleeding)	1. In patients undergoing major orthopedic surgery with increased risk of bleeding (≥2 risk factors), we suggest using IPCD or no thromboprophylaxis. **2.** In patients undergoing major orthopedic surgery, we suggest against using IVC filter placement for primary prevention over no prophylaxis in patients with increased risk of bleeding or contraindication to both IPCD and pharmacologic thromboprophylaxis.	• Patients who place a high value on avoiding the discomfort and inconvenience of IPCD and a low value on avoiding a small absolute increase in bleeding with pharmacologic agents when only one bleeding RF is present (e.g. antiplatelet agent use) are likely to choose pharmacologic thromboprophylaxis over IPCD.

[92] American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients; Blood Adv (2019) 3 (23): 3898–3944

[93] Direct quote from Chest-2012-Falck-Ytter-Prevention of VTE in Orthopedic Surgery Patients – e290S.

[94] Range of 1.8-2.3 not recommended in ACCP guidelines, but is used locally by some orthopedists due to concern with bleeding risk after joint replacement surgery.

Arthroscopic knee procedures or isolated lower leg injuries requiring leg immobilization without prior VTE	**No prophylaxis is recommended**	• Elective knee arthroscopy does not require post procedure prophylaxis if early ambulation is possible and no other thromboembolic risk factors present.
Arthroscopic knee procedures or isolated lower leg injuries requiring leg immobilization with prior VTE	**Option 1:** LMWH (preferred) started 12+ hours before surgery or 12+ hours after surgery at full prophylactic dose [enoxaparin (Lovenox) 30 mg bid or 40 mg qd if twice daily dosing not feasible].	• With history of VTE, prophylaxis based on risk recommended. • Anticoagulation should be continued for at least 10-14 days, and suggested up to 35 days (5 weeks), based on patient's thrombotic risk, as determined by the treating orthopedist. • See above comment regarding use of aspirin for VTE prophylaxis. • Although not in CHEST guidelines, it is reasonable to consider treating first with LMWH followed by dose-adjusted warfarin or aspirin.
	Option 2: Fondaparinux (Arixtra) 2.5mg/day started 6-8 hours after surgery	
	Option 3: Adjusted dose warfarin started before surgery or on the evening after surgery (INR target of 2.5, range of 2-3 or INR target of 2.0, range of 1.8-2.3 per orthopedist's recommendation)[95]	
	Option 4: LDUH 5000 units every 8 to 12 hours	
	Option 5: Aspirin ~160mg daily	
	Option 6: Warfarin started before surgery or on the evening after surgery with INR target of 2.5, range of 2-3 or INR target of 2.0, range of 1.8-2.3 per orthopedist's recommendation)[96]	

[95] Ibid.
[96] Ibid.

Appendix 9: HYPERCOAGULABILITY EVALUATION[97]

Definition of High Risk Thrombophilia:

1. In patients with at least one spontaneous event, high-risk thrombophilia is defined by one of the following:
   a. Antithrombin deficiency,
   b. Antiphospholipid syndrome, or
   c. Two or more medium-risk genetic mutations including heterozygous protein C, S or antithrombin deficiencies, or
   d. Either heterozygous Factor V Leiden or heterozygous prothrombin gene mutation combined with another significant thrombophilia.
2. Patients with one spontaneous event and low risk thrombophilia are temporarily at high risk during thrombogenic situations, such as when undergoing high risk surgery and a period of prolonged immobilization, including long plane flights (generally defined as at least seven hours).

Decisions regarding thrombophilia evaluation:[98] [99]

1. **Most patients with VTE should not be tested for thrombophilia, since the results of testing will rarely influence management decisions.**
2. **Patients for whom thrombophilia testing may be considered:**
   a. Patients with unprovoked VTE who wish to stop anticoagulation after initial treatment and testing may change the decision. However, a negative thrombophilia evaluation is not a sufficient basis to stop anticoagulation following an unprovoked VTE in a patient with low bleeding risk willing to continue therapy.
   b. Patients with VTE in unusual locations, specifically cerebral or splanchnic veins.
   c. Women with a first degree relative with hereditary thrombophilia or multiple family members with history of VTE and who are contemplating pregnancy, if the result would change VTE prophylaxis decisions.
   d. Patients with a history of VTE who wish to assess risks that may be posed to family members planning pregnancy.
   e. Patients with multiple family members with VTE; these patients are more likely to have antithrombin deficiency, and when also having a personal history of VTE, may have highest risk of VTE. The results of thrombophilia testing may affect management decisions, such as bridging when warfarin is held, INR is well below therapeutic range, or in situations of increased clotting risk.
   f. Patient with repeated discrepancies between capillary and venous INR readings (consider antiphospholipid testing).
3. **Patients who do NOT usually need thrombophilia testing:**
   a. Patients with provoked VTE. Thrombophilia testing does not affect decisions about duration of anticoagulation after provoked VTE, so should not routinely be done.
   b. Patients with unprovoked VTE who are pursuing long-term anticoagulation (as generally recommended) or who cannot tolerate long-term anticoagulation.
   c. Women not contemplating pregnancy and all men with no history of VTE and a single family member with inherited thrombophilia.
   d. Women contemplating pregnancy who have had a history of VTE.

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[97] Review article with case presentations: Hypercoagulability: Too Many Tests, Too Much Conflicting Data; Bauer, KA, Rosendaal, FR, Heit, JA; Hematology: 2002; 1:353-368
[98] Stevens, SM et al; Guidance for the evaluation and treatment of hereditary thrombophilia; J Thromb Thrombolysis (2016) 41:154–164
[99] JM Connors; Thrombophilia Testing and Venous Thrombosis; N Engl J Med 2017; 377:1177-1187

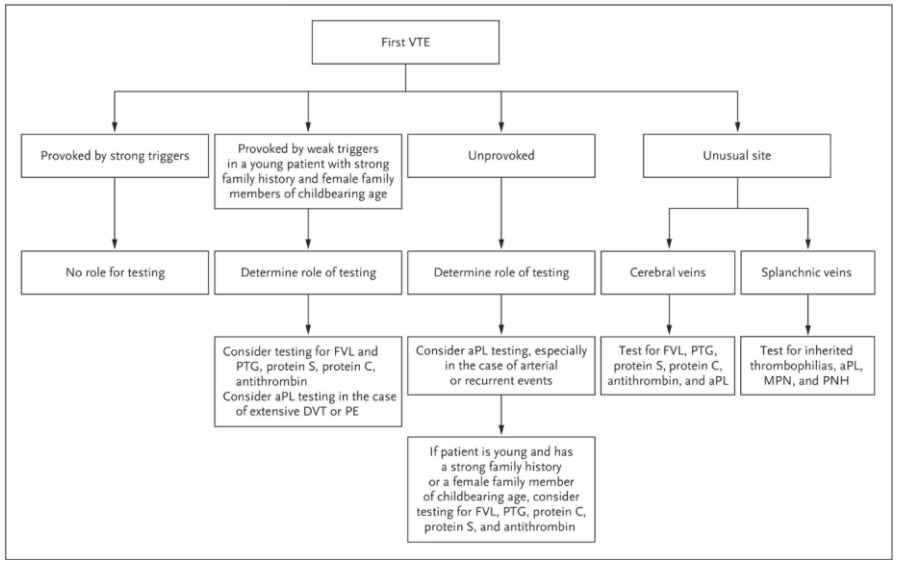
e. In patients with a history of unprovoked VTE (with or without thrombophilia), relatives have an excess risk of VTE, and should be advised of this excess risk. However, these relatives do not require testing, since the excess risk is already conferred by the family history of VTE. Note that this rule applies even when the relative is considering oral contraceptives or estrogen use. Possible exception: see 2c above.

Factors associated with hereditary thrombophilia:

1. First VTE at young age (less than 40 to 50 years of age), particularly associated with weak or no provoking factors
2. Recurrent VTE, any cause and any location
3. Strong family history of VTE – risk increases with multiple family members and early age of family members with VTE
4. VTE in unusual location (such as central nervous system or splanchnic veins)
5. History of three or more unexplained spontaneous abortions and contemplating another pregnancy

Note that the presence of any of the first 4 factors, though associated with a higher risk of hereditary thrombophilia, would confer the same risk of recurrent VTE with or without having positive testing for thrombophilia. The 5th factor confers a risk of recurrent spontaneous abortion regardless of testing, though evaluation in this case may inform on management of the patient.

Suggested algorithm for Selecting Patients with VTE for thrombophilia testing:



Algorithm present as Figure 1 in JM Connors; Thrombophilia Testing and Venous Thrombosis; N Engl J Med 2017; 377:1177-1187

Timing of Testing:

1. Testing should not be done at time of VTE diagnosis or during the 3-month treatment course. Ideally, complete testing 3 weeks after stopping anticoagulation (warfarin stopped for at least 2 weeks, DOACs stopped for at least 2 days, and for antithrombin levels UFH or LMWH stopped for at least 24 hours).
2. Note that pregnancy, sex and estrogen use reduce the levels of Protein S. Use of sex-specific reference intervals, and testing prior to pregnancy or while not receiving estrogen preparations is preferred.

Other important considerations:

1. ***Consideration of stopping anticoagulation after acute treatment of DVT or PE of undetermined cause***. Patients with unprovoked VTE have a high risk of recurrent VTE regardless of the presence of a hereditary thrombophilia, so these patients should always be considered for extended and perhaps lifetime anticoagulation. Risk of recurrent VTE in this population approaches 30% in the 3 years following stopping anticoagulation. When a patient has a high bleeding risk, however, or has already had bleeding, the risks of a recurrent bleed may exceed even the high risk of recurrent VTE. In these cases, the presence of a high-risk thrombophilia may be the deciding factor. When bleeding risk can be mitigated by other measures, such as institution of PPI therapy in the context of a history of upper GI bleeding, continued anticoagulation should probably occur. When high bleeding risk persists, anticoagulation should probably be discontinued. Note that this analysis may proceed regardless of the presence of a high-risk thrombophilia. However, when results of this evaluation include the presence of high risk thrombophilia, despite the lack of outcome evidence in favor of testing, they may tip the balance toward continuing anticoagulation. See Appendix 1: Duration of Anticoagulation after Unprovoked DVT/PE and Appendix 11: Considerations for Anticoagulant Selection in Atrial Fibrillation and VTE Treatment.
2. ***Need for determination of use of LMWH for bridging in warfarin patients with DVT of undetermined cause receiving extended treatment*.** There is no current evidence that the presence or absence of a hereditary thrombophilia affects the risk of holding anticoagulation in times of expected or unanticipated lack of therapeutic anticoagulation. In fact, there is no current evidence that bridging for low INR values affects outcome in these cases. The contribution of the presence of high-risk thrombophilia to the risk of recurrent VTE in short-term lapses of anticoagulation therapy has never been determined. However, current standard of care suggests that we should consider bridging patients at highest risk of recurrent VTE. In these cases that presence of a high-risk thrombophilia, when known, may alter consideration of bridging when INR is low or expected to be low around the time of a procedure. We do not suggest that patients should be tested in anticipation of this clinical scenario. However, if testing has already been completed, clinicians evaluating the need for bridging in these circumstances may weigh the evidence of risk, including consideration of known positive tests for hereditary thrombophilia.
3. ***Concern with accuracy of ISTAT and other capillary point of care tests:*** The presence of lupus anticoagulant, anticardiolipin and other anti-phospholipid antibodies may prevent accurate determination of INR by the ISTAT and other capillary point of care tests. When these antibodies are known, the capillary test should not be used, since results may be falsely elevated above the actual INR. When repeated significant disparities (at least 2.0, especially if capillary INR is below 6.0) between capillary and venous INRs are noted, testing for anticardiolipin and other antiphospholipid antibodies (noted in blue below) should be considered.

1. **The presence of active cancer already confers increased risk of VTE.** Testing for hereditary thrombophilia is rarely needed in these patients.
2. **The plan for surgery mainly increases risk for VTE based on the immobilization conferred following surgery. The need for testing for hereditary thrombophilia is rarely needed in these cases. When a high risk thrombophilia is already known, it should be taken into consideration.**

3. **Patients with antithrombin deficiency** may require acute treatment with antithrombin concentrate in the setting of a new event or surgery, due to inadequate response to heparin products in this setting.[100] This consideration may indicate use of available testing information, but should not be the reason for routinely testing patients in the anticipation of surgery.
4. **In patients with known protein C deficiency**, starting warfarin may further deplete factor C and result in secondary acute hypercoagulability and skin necrosis. To prevent this complication, heparin should be started in full therapeutic dose before starting warfarin, and warfarin should be started in low initial doses.[101] This consideration may affect testing in patients with known family history of factor C deficiency who are about to start warfarin. Since treatment may need to occur before testing results are available, patients should be covered by adequate LMWH before institution of treatment with warfarin.

5. Diagnosis of antiphospholipid syndrome requires confirmation of abnormal results after at least 12 weeks, since transient elevations of these antibodies may occur with various infections. In the presence of high clinical suspicion with strongly positive initial titer and negative repeat, a third titer several weeks later should be done before excluding the diagnosis.[102] **Revised Sapporo Criteria for Diagnosis of APS:**

APS is present if at least one of the two clinical criteria and at least one of three laboratory criteria are met:

- **Clinical Criteria:**
  - Vascular thrombosis: one or more documented clinical episodes of arterial or venous thrombosis in any organ or tissue (documented by means of imaging or histopathological assessment) in the absence of vasculitis.
  - Pregnancy complication:
    - Unexplained death of a morphologically normal fetus at or beyond week 10 of gestation
    - Premature birth of a morphologically normal neonate before week 34 of gestation as a result of eclampsia, severe preeclampsia, or placental insufficiency
    - Three or more unexplained, consecutive, spontaneous abortions before week 10 of gestation, not related to chromosomal or anatomical abnormalities in the parents
- **Laboratory Criteria:**
  - Lupus anticoagulant assay
  - IgG or IgM anticardiolipin antibody test
  - IgG or IgM anti-beta-2 glycoprotein 1 antibody test

At least one laboratory test must be positive on two occasions at least 12 weeks apart. For ELISA-based tests, results should be at least 40 units or in the 99th percentile. Ideally, in addition to ELISA-based tests, two in vitro clot-based assays should be performed to determine the presence of a lupus anticoagulant.

Adapted from JM Connors; Thrombophilia Testing and Venous Thrombosis; N Engl J Med 2017; 377:1177-1187

Evaluation:

Note that Factor V Leiden and prothrombin gene mutation mainly have significance in decision-making when homozygous and/or heterozygous combined with other significant thrombophilias. Homozygous or heterozygous state must be specified in all patient assessments. ***Specific tests:***

[100] Schwartz RS, Bauer KA, Rosenberg RD, et al. Clinical experience with antithrombin III concentrate in treatment of congenital and acquired deficiency of antithrombin. The Antithrombin III Study Group. Am J Med 1989; 87:53S

[101] Zauber NP, Stark MW. Successful warfarin anticoagulation despite protein C deficiency and a history of warfarin necrosis. Ann Intern Med 1986; 104:659.

[102] Erkan et al; Diagnosis of the antiphospholipid syndrome; UpToDate; Topic 4678 Version 28.0; Apr 10, 2018

Test	Is test reliable on warfarin?	Is test reliable on heparin?	Possible indications for testing:	Comments:
Antiphospholipid (aPL) Tests				
ANTI CARDIOLIPIN ANTIBODY IgG/IgM [LAB197]	Yes	Yes	Consider ordering aPL tests for: • Unprovoked VTE, especially if arterial or recurrent events. • Extensive DVT or PE provoked by weak triggers in young patient with strong family history and female family members of childbearing age. • Thrombosis at unusual site (such as cerebral or splanchnic veins). • Certain specific adverse outcomes related to pregnancy, regardless of the history of VTE (e.g., fetal loss after 10th week of gestation, recurrent early miscarriages, intrauterine growth restriction, severe preeclampsia) • Otherwise unexplained thrombocytopenia or prolonged aPTT[103] Confirm positive tests after 12 weeks.	Can be done while patient on either warfarin or heparin.
ANTI BETA-2-GLYCOPROTEIN I ANTIBODY IgA/IgG/IgM [LAB127]	Yes	Yes		Can be done while patient on either warfarin or heparin.
LUPUS ANTICOAGULANT EVALUATION W/REFLEX (FUNCTIONAL ASSAY) [LAB684]	*Yes, if INR <3.5*	*No on UFH Yes on LMWH with anti-Xa therapeutic*		Best general screen for anti-phospholipid antibodies. Do not order if patient currently on heparin or oral factor Xa inhibitors (apixaban, edoxaban, or rivaroxaban), since may be misclassified as having lupus anticoagulant.
Inherited Thrombophilias				
ANTITHROMBIN III ACTIVITY W/RFLX ANTIGEN [LAB73]	Yes	No	Consider ordering tests for inherited thrombophilia for: • Unprovoked VTE in young patient with strong family history and female family members of childbearing age • VTE provoked by weak triggers in young patient with strong family history and female family members of childbearing age.	May be reduced by thrombosis, so should be done after clot has stabilized, off heparin. Considered high-risk thrombophilia, with 60% chance of recurrent VTE. Treatment with most DOACs may cause overestimates of level.[104]
FACTOR V R506Q LEIDEN [LAB418]	Yes	Yes		Can be done while patient on either warfarin or heparin. More common in Caucasians than other racial groups.[105]
PROTEIN C ACTIVITY [LAB883]	No*	Yes		*May be decreased by warfarin; if normal while patient is on warfarin, there is likely no

[103] Erkan et al; Diagnosis of the antiphospholipid syndrome; UpToDate; Topic 4678 Version 28.0; Apr 10, 2018
[104] Bauer et al; Antithrombin deficiency; UpToDate; Topic 1360; Version 26.0; May 1, 2018
[105] Carrier frequency 2.21% in 407 Hispanic Americans, 1.23% in 650 African Americans, 0.45% in 442 Asian Americans, 1.25% in 80 Native Americans Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for VTE screening. JAMA. 1997 Apr 23-30; 277(16):1305-7.

			• Thrombosis at unusual site (such as cerebral or splanchnic veins). • When family history of specific thrombophilia present and testing is indicated, target testing toward that thrombophilia.	deficiency. May be increased by DOAC.[106] Also, see footnote[107]. Factor V Leiden mutation may give falsely low values. Deficiency associated with warfarin-induced skin necrosis.
PROTEIN S ACTIVITY [LAB889]	No*	Yes		*May be decreased by warfarin; if normal while patient is on warfarin, there is likely no deficiency. May be increased by DOAC.[82] Also, see footnote[83]. Factor V Leiden mutation may give falsely low values. Deficiency associated with warfarin-induced skin necrosis.
PROTHROMBIN (FACTOR II) GENE (20210GA) MUTATION ANALYSIS [LAB893]	Yes	Yes		Can be done while patient on either warfarin or heparin. Heterozygous state results in relatively low-risk thrombophilia, unless FVL or other thrombophilia present.[108]
Myeloproliferative Neoplasms (MPN)				
CBC W/DIFF (LAB547)	Yes	Yes	CBC is required whenever anticoagulants are anticipated or used, but especially important to use as screening for MPN with thrombosis at unusual sites, such as splanchnic veins	
Paroxysmal Nocturnal Hemoglobinuria (PNH)				
CBC W/DIFF (LAB547), RETIC COUNT [LAB923], LDH [LAB564], BILIRUBIN TOTAL W/RFLX [LAB134]	Yes	Yes	Screening for PNH should occur with thrombosis at unusual sites, such as splanchnic veins.	

[106] Bauer et al; Protein S deficiency; UpToDate; Topic 1357 ; Version 18.0; Nov 10, 2017 ;

[107] If plasma levels of antithrombin and protein S and C are obtained at presentation prior to the administration of anticoagulant therapy and are well within the normal range, then a deficiency of these proteins is excluded. In contrast, a low concentration in the setting of acute thrombosis must be confirmed by repeat testing after anticoagulation has been discontinued.

[108] Baseline thrombotic risk increases 3.8 times with Prothrombin Gene mutation and 4.9 times with heterozygous FVL; increase in risk 20.0 times when both disorders present Emeriti J, Rosendaal FR, Cattaneo M, Margaglione M, De Stefano V, Cumming T, Arruda V, Hillarp A, Reny JL. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism. Thromb Haemost. 2001 Sep; 86(3):809-16.

Effect of Direct Oral Anticoagulants on Laboratory Testing or Interpretation[109]:

COAGULATION ASSAY	DIRECT FACTOR XA INHIBITOR*	DIRECT THROMBIN INHIBITOR**
Fibrinogen Clauss method	No effect	Potential false underestimation, depending on drug concentration and assay reagent
Thrombin time	No effect	Prolonged
Antithrombin activity **FXa-based** **FIIa-based**	 False overestimation No effect	 No effect False overestimation
Protein C activity **Clot-based** **Chromogenic-based**	 False overestimation No affect	 False overestimation No effect
Protein S activity (clot-based)	False overestimation	False overestimation
Free protein S antigen immunoassay	No effect	No effect
Lupus anticoagulant Panel (final interpretation)	False Positive, depending on assay or reagent	False Positive, depending on assay or reagent
Cardiolipin and Beta-2-glycoprotein I (β2GPI) antibodies	No effect	No effect
Activated protein C resistance ratio based in aPTT plus factor V-deficient plasma	False elevation	False elevation
von Willebrand antigen and activity	No effect	No effect
D- Dimer (quantitative)	No effect	No effect

* **Direct Xa inhibitors** include rivaroxaban, apixaban, edoxaban, and betrixaban
**** Direct thrombin inhibitors** include dabigatran, argatroban, and bivalirudin

[109] Adapted from Adcock, D.M and Gosselin, R. Direct Oral Anticoagulants (DOACs) in the Laboratory: 2015 Review Thrombosis Research 136 (2015) 7–12

Appendix 10: apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa), edoxaban (Savaysa) and betrixaban (Bevyxxa)

Atrius formulary Considerations:

- **Stroke prophylaxis in NVAF**: apixaban (Eliquis) or rivaroxaban (Xarelto) are formulary DOACs considered 1st line options in addition to warfarin
- **VTE Treatment and prevention of recurrence**: apixaban (Eliquis) or rivaroxaban (Xarelto) are formulary DOACs considered 1st line options in addition to warfarin (+ enoxaparin).
- **VTE prophylaxis after joint replacement therapy**: enoxaparin (generic Lovenox) is preferred over other treatments. Apixaban (Eliquis) and rivaroxaban (Xarelto) remain alternative agents in addition to warfarin currently included in the Atrius formulary.

Edoxaban (Savaysa) and dabigatran (Pradaxa) are non-formulary[85], however can be used if most appropriate option for a particular patient.

- Dabigatran has higher rates of dyspepsia leading to discontinuation and has demonstrated higher rates of gastrointestinal bleeding and higher rates of major bleeding (excluding ICH) in elderly patients compared to warfarin. As a twice-daily medication, it has no compliance advantages over apixaban and when used for treatment of VTE, unlike apixaban and rivaroxaban, dabigatran requires initial parenteral therapy.
- Edoxaban is not recommended for patients with normal renal function (CrCl >95mL/min) for stroke prophylaxis in NVAF due to findings of an increased rate of stroke compared to warfarin in this patient population in the ENGAGE-AF TIMI trial. It is also not approved for prevention of recurrence of VTE or VTE prophylaxis after joint replacement surgery and has not demonstrated any specific efficacy or safety advantages over apixaban or rivaroxaban.

Comparative Efficacy and Safety of DOACs from Pivotal Clinical Trials for NVAF and VTE Treatment:

STROKE PREVENTION IN NVAF: DOAC vs. WARFARIN				
	APIXABAN 5MG BID	**RIVAROXABAN 20MG QD**	**DABIGATRAN 150MG BID**	**EDOXABAN 60MG QD**
Pivotal study DOAC vs. warfarin (INR 2-3)	ARISTOTLE[110]	ROCKET-AF[111]	RE-LY[112]	ENGAGE-AF[113]
Mean CHADS2 score	2.1	3.5	2.1	2.8
Mean time in therapeutic range	62%	55%	64%	65%
Efficacy: all stroke/systemic embolism	Superior	Non-inferior	Superior	Non-inferior
Efficacy: ischemic stroke	No significant difference	No significant difference	Significantly lower	No significant difference
Efficacy: hemorrhagic stroke	Significantly lower	Significantly lower	Significantly lower	Significantly lower
Safety: major bleeding	Significantly lower	No significant difference	No significant difference	Significantly lower
Safety: GI bleeding	No significant difference	Significantly higher	Significantly higher	Significantly higher
All-cause mortality	Significantly lower	Favorable trend	Favorable trend	Favorable trend

[110] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-992.
[111] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891.
[112] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
[113] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104.

VTE TREATMENT: DOAC vs. WARFARIN + ENOXAPARIN						
	APIXABAN	RIVAROXABAN		DABIGATRAN		EDOXABAN
Pivotal study DOAC vs. warfarin (INR 2-3)	AMPLIFY[114]	EINSTEIN DVT[115]	EINSTEIN PE[116]	RE-COVER[117]	RE-COVER II[118]	Hokusai VTE[119]
Mean age	57 years	56 years	58 years	55 years	55 years	56 years
Mean time in therapeutic range	61%	58%	63%	60%	57%	63%
Efficacy: recurrence of symptomatic VTE	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Safety: major bleeding	Superior	No significant difference	Significantly lower	No significant difference	No significant difference	No significant difference
Safety: major + non-major clinically relevant bleeding	Significantly lower	No significant difference	No significant difference	Significantly lower	Significantly lower	Superior

Conclusion: DOACs are either non-inferior or superior to warfarin for prevention of stroke and systemic embolism in NVAF and for recurrence of symptomatic VTE in the treatment of acute VTE. DOACs demonstrated similar or significantly lower risks of major bleeding (including lower risk of intracranial hemorrhage), despite a higher risk of GI bleeding for patients with NVAF (except apixaban, which was found to have no significant difference in GI bleeding).

Comparative Pharmacokinetic Properties of DOACs and Warfarin:

	WARFARIN	APIXABAN	RIVAROXABAN	DABIGATRAN	EDOXABAN
Target of activity	VKORC1	Factor Xa	Factor Xa	Thrombin	Factor Xa
Time to peak anticoagulant effect	72-96 hours	3-4 hours	2-4 hours	1-3 hours	1-2 hours
Bioavailability	100%	50%	15mg/20mg: 66% without food, 80-100% with food	3-7%	62%
Prodrug	No	No	No	Yes	No
Renal clearance	None	27%	35%	80%	50%
Plasma protein binding	99%	87%	95%	35%	55%
Dialyzable	No	No	No	50-60% (in part dialyzable)	No
Liver metabolism: CYP3A4 involved	Minor	~25%	~18%	No	Minimal (<4%)
Absorption with food	No effect (other interactions secondary to vitamin K content)	No effect	+ 39% more	No effect	6-22% more; minimal effect on exposure
Elimination half-life	~40 hours	~12 hours	5-9 hours (young) 11-13 hours (elderly)	12-17 hours	10-14 hours

[114] Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808.
[115] Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510
[116] Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297.
[117] Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.
[118] Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772.
[119] Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415

Other			Intake of 15mg/20mg with food mandatory	Dyspepsia (5-10%)	

Advantages and Disadvantages of DOACS vs Warfarin:

ADVANTAGES of DOAC	DISADVANTAGES of DOAC
No INR monitoring required – greater patient convenience	No reliable, readily available measurement assay – lack of monitoring may result in non-adherence or inability to ensure adequate levels of anticoagulation in special populations
Fixed dosing without need for frequent dose adjustments	Less flexibility in dosing
Rapid onset - generally eliminates need for bridging (except dabigatran and edoxaban require initial parenteral anticoagulation for 5-10 days for acute VTE treatment)	Higher out-of-pocket costs/copays
Short half-life (advantageous for invasive procedures or in the setting of active bleed)	Short half-life (mandates strict adherence)
Lower incidence of intracranial hemorrhage vs warfarin	Possible higher risk of GI bleeding (rivaroxaban, dabigatran, edoxaban)
Fewer drug-drug and drug-diet interactions	Fewer studies and approved indications

MEASURING DOAC LEVELS AND EFFECT ON COAGULATION ASSAYS:

There are currently no readily available routine laboratory tests that can reliably monitor the anticoagulant effect of DOAC's in a manner similar to how the INR is used to monitor warfarin therapy, or how the aPTT is used for IV unfractionated heparin therapy. These laboratory tests should NOT be used to monitor the anticoagulant effect of a DOAC.

Some institutions (but not Atrius) do have dedicated anti-Factor Xa chromogenic assays available to measure plasma concentrations of these inhibitors using validated calibrators. However, there are no established standards for interpreting test results.

If DOAC plasma monitoring is performed, it is recommended to check peak levels after reaching a steady state on DOAC (requiring at least 3 days of regular medication) and to draw levels ~3-4 hours after taking the DOAC. To check trough levels, draw just before the next DOAC dose is taken. Quest diagnostics does have available information on testing for apixaban and rivaroxaban levels:
--> Quest: Testing Apixaban levels
--> Quest: Testing Rivaroxaban levels

For Effect on Coagulation Assays: NOACs/DOACs: Effect on Coagulation Tests.
Specific assays: refer to **Table 9 Plasma levels and coagulation assays in patients treated with non-vitamin K antagonist oral anticoagulants** of The 2018 European Heart Journal Practical Guide on the Use of non-Vitamin K antagonists in patients with atrial fibrillation

COMPLIANCE WITH LAB MONITORING FOR ANTICOAGULATION PATIENTS

NOTE: The Cockcroft-Gault equation should be used when calculating renal function, as clinical trials evaluating all approved DOACs used this equation to determine dosing or exclusion. Xarelto, Pradaxa, and Savaysa clinical trials used **actual body weight** to calculate CrCl, while the Eliquis trials did

not specify which weight was used. Clinical judgment must be used when calculating CrCl in overweight/obese patients. Using actual body weight may overestimate renal function in this population; therefore use of an *adjusted* body weight may be a more practical approach. Type ".CreatCl" into a progress note for patient in Epic to estimate CrCl (per Cockcroft-Gault) according to various body weights, depending on patient BMI. This calculator can also be used, especially for overweight/obese patients

Use of DOACs in Severe Renal Impairment (CrCl <30mL/min):

DVT/PE Treatment and Prophylaxis Indications:

- **Apixaban (Eliquis)** efficacy/safety has not been evaluated in patients with CrCl <25mL/min or Scr >2.5mg/dL. The manufacturer does not recommend specific dose adjustments on the basis of renal function. Given the lack of adequate evaluation in patients with poor renal function, any use must include great caution, and probably be restricted to patients who absolutely cannot take warfarin. For these patients, apixaban (Eliquis) may be the preferred DOAC option, as it relies least on renal clearance.
- **Rivaroxaban (Xarelto):** In the EINSTEIN trials, patients with CrCl values <30 mL/min at screening were excluded from the studies, but administration of XARELTO is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 15 to <30 mL/min. Avoid the use of XARELTO in patients with CrCl <15 mL/min. Discontinue XARELTO in patients who develop acute renal failure while on treatment.
- **Dabigatran (Pradaxa)** should be avoided as recommended by manufacturer.
- **Edoxaban (Savaysa)** efficacy/safety has not been evaluated in patients with CrCl <30mL/min. Therefore, edoxaban (Savaysa) should be used with great caution and warfarin use should be considered in patients with CrCl 15-30mL/min. Note: edoxaban (Savaysa) should be avoided if CrCl <15mL/min.

Non-valvular atrial fibrillation (NVAF) Indications:

- **Apixaban (Eliquis)** efficacy/safety has not been evaluated in patients with CrCl <25mL/min or Scr >2.5mg/dL. The manufacturer does not recommend specific dose adjustments on the basis of renal function. Given the lack of adequate evaluation in patients with poor renal function, any use must include great caution, and probably be restricted to patients who absolutely cannot take warfarin. For these patients, apixaban (Eliquis) may be the preferred DOAC option, as it relies least on renal clearance. In end-stage renal disease (CrCl <15 or dialysis-dependent), individualized decision-making is appropriate with suggestion to use well-managed warfarin with TTR > 65% (CHEST-2018). For patients with non-valvular AF who have a CHA2DS2-VASc score of ≥2 in men or ≥3 in women and who have ESRD, apixaban (Eliquis) may be used for patients receiving hemodialysis at the discretion of the patient's nephrologist. Dabigatran, rivaroxaban, or edoxaban are not recommended in the setting of ESRD (AHA/ACC/HRS-2019)
- **Rivaroxaban (Xarelto):** In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl <30 mL/min were not studied, but administration of XARELTO 15 mg once daily is expected to result in serum concentrations of rivaroxaban similar to those in patients with moderate renal impairment
- **Dabigatran (Pradaxa)** should be avoided if CrCl <30mL/min, as the reduced dose of 75mg BID has not actually been evaluated for safety and efficacy. Since dabigatran (Pradaxa) relies most on renal clearance, an alternative DOAC should be used when warfarin cannot be used

- **Edoxaban (Savaysa)** efficacy and safety have not been evaluated in patients with CrCl <30mL/min. Edoxaban (Savaysa) should be used with great caution in patients with CrCl 15-30mL/min, and warfarin use should be considered in these patients. **Rivaroxaban (Xarelto) and Edoxaban (Savaysa)** should be avoided if CrCl <15mL/min.

DOAC	Indication						
	Non-valvular Atrial Fibrillation	**DVT/PE Treatment**	**DVT/PE Prevention of Recurrence**	**DVT/PE Prophylaxis Post Knee Replacement**	**DVT/PE Prophylaxis Post Hip Replacement**	**Stable coronary artery disease or peripheral artery disease (prevention of major cardiovascular events):**	**Prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding**
Apixaban (Eliquis)[120] ***Atrius preferred DOAC***	5mg twice daily 2.5mg twice daily if **≥2** of the following: • Age ≥ 80 years • Body weight ≤ 60 kg • Scr ≥ 1.5mg/dL*	10mg twice daily for 7 days, then 5mg twice daily	2.5mg twice daily after at least 6 months of treatment for DVT/PE**	2.5mg twice daily for 12 days Administer first dose 12-24 hours after surgery	2.5mg twice daily for 35 days Administer first dose 12-24 hours after surgery.	Not FDA approved for indication.	Not FDA approved for indication
Rivaroxaban (Xarelto)[121] ***Atrius preferred DOAC***	CrCl > 50 mL/min: 20mg once daily with evening meal CrCl ≤ 50 mL/min: 15mg once daily with evening meal	15mg twice daily with food for 21 days, then 20mg once daily with food Avoid use if CrCl <15 mL/min	10mg daily after at least 6 months of treatment for DVT/PE** Avoid use if CrCl <15 mL/min	10mg once daily (with or without food) for 12 days Administer first dose 6 to 10 hours after surgery.	10mg once daily (with or without food) for 35 days Administer first dose 6 to 10 hours after surgery.	2.5 mg twice daily; administer in combination with daily low dose aspirin. No dose adjustment needed based on CrCl	CrCl ≥ 15 mL/min: 10 mg daily in hospital and after hospital discharge, for total recommended duration of 31-39 days Avoid use if CrCl <15 mL/min

[120] Eliquis Prescribing Information, Bristol-Myers Squibb Co., 2016
[121] Xarelto Prescribing Information, Janssen Pharmaceuticals, Inc. 2017

				Avoid use if CrCl <15 mL/min	Avoid use if CrCl <15 mL/min		
Dabigatran (Pradaxa)[122] ***Atrius non-formulary***	CrCl > 30 mL/min: 150mg twice daily CrCl 15-30 mL/min***: 75mg twice daily *(dose not evaluated in phase III trials)*	150mg twice daily after 5-10 days of parenteral anticoagulation. Not recommended if CrCl <30 mL/min.	150mg twice daily Not recommended if CrCl <30 mL/min.	Not FDA approved for indication.	110mg once daily 1-4 hours after surgery, then 220mg taken once daily for 28-35 days. If not started on the day of surgery, initiate with 220mg once daily. Not recommended if CrCl <30 mL/min.	Not FDA approved for indication.	Not FDA approved for indication.
Edoxaban (Savaysa)[123] ***Atrius non-formulary***	Do not use if CrCl >95mL/min CrCl >50-≤95mL/min: 60mg once daily CrCl 15-50 mL/min***: 30mg once daily	60mg once daily after 5-10 days of parenteral anticoagulation. CrCl 15-50 mL/min OR body weight ≤ 60kg: 30mg once daily after 5-10 days of parenteral anticoagulation.	Not FDA approved for indication.	Not FDA approved for indication.	Not FDA approved for indication.	Not FDA approved for indication.	Not FDA approved for indication.

[122] Pradaxa Prescribing Information, Boehringer Ingelheim Pharmaceuticals, Inc. 2018
[123] Savaysa Prescribing Information, Daiichi Sankyo Co., LTD, 2017

Betrixaban (Bevyxxa) **Atrius non-formulary**	Not FDA approved for indication	Not FDA approved for indication	Not FDA approved for indication	Not FDA approved for indication	Not FDA approved for indication	Not FDA approved for indication	CrCl ≥ 30 mL/min: single dose of 160 mg, followed by 80 mg once daily with food, for a recommended duration of 35-42 days CrCl ≥15 to < 30 mL/min: single dose of 80 mg followed by 40 mg once daily, for a recommended duration of 35-42 days

* The efficacy and safety of apixaban (Eliquis) has not been evaluated in patients with a CrCl <25mL/min or Scr >2.5mg/dL
** Clinical trials evaluating reduced doses of apixaban (2.5mg BID) and rivaroxaban (10mg daily) for VTE prevention of recurrence included only patients for whom there was uncertainty regarding the need for continued anticoagulation. Patients with clear indications for long term therapeutic anticoagulation (e.g., multiple episodes of unprovoked DVT or PE, documented anti-phospholipid antibodies) were excluded. Questions of whether or not a patient can reduce dose after 6 months of therapy should be reviewed with a consultant.
***The efficacy and safety of rivaroxaban (Xarelto), dabigatran (Pradaxa), and edoxaban (Savaysa) have not been evaluated in patients with a CrCl <30 mL/min

DOAC DRUG-DRUG INTERACTIONS

APIXABAN (ELIQUIS)			
DRUG CLASS	**TYPE OF INTERACTION**	**INDICATION**	**RECOMMENDATIONS**
Combined P-gp inhibitor and *strong* CYP3A4 inhibitor*	***Significant*** ↑ in apixaban concentration	All indications	**5 or 10 mg twice daily:** ↓ dose by 50% **2.5 mg twice daily:** Avoid use
Combined P-gp inhibitor and *moderate* CYP3A4 inhibitor**	***Moderate*** ↑ in apixaban concentration *Concentration may be significantly ↑ in patients with impaired renal function*	All indications	No specific dose adjustment recommended by manufacturer. Use with caution.
Combined P-gp inducer and *strong* CYP3A4 inducer†	***Significant*** ↓ in apixaban concentration	All indications	Avoid use

RIVAROXABAN (XARELTO)

DRUG CLASS	TYPE OF INTERACTION	INDICATION	RECOMMENDATIONS
Combined P-gp inhibitor and *strong* inhibitor of CYP3A4*	***Significant*** ↑ in rivaroxaban concentration	All indications	Avoid use
Combined P-gp inhibitor and/or *moderate* CYP3A4 inhibitor**	***Moderate*** ↑ in rivaroxaban concentration *Concentration may be significantly ↑ in patients with impaired renal function*	All indications	**CrCl 15 to <80 mL/min:** Use only if the potential benefit justifies the potential risk **CrCl <15 mL/min**: Avoid use
Combined P-gp inducer and *strong* CYP3A4 inducer†	***Significant*** ↓ in rivaroxaban concentration	All indications	Avoid use

*Combined P-gp Inhibitor and *Strong* CYP3A4 Inhibitor *(list not exhaustive)*	**Combined P-gp Inhibitor and *Moderate* CYP3A4 Inhibitor *(list not exhaustive)*	†Combined P-gp Inducer and *Strong* CYP3A4 Inducer *(list not exhaustive)*
Ketoconazole Itraconazole Ritonavir Lopinavir/ritonavir Indinavir Nelfinavir Conivaptan Posaconazole Saquinavir Grapefruit juice Telaprevir	Dronedarone Verapamil Diltiazem Erythromycin Cyclosporine Tamoxifen	Rifampin Carbamazepine Phenytoin Phenobarbital St. John's wort

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with apixaban or rivaroxaban.

DABIGATRAN (PRADAXA)			
DRUG CLASS	**TYPE OF INTERACTION**	**INDICATION**	**RECOMMENDATIONS**
Inhibitors of P-gp*	***Variable*** ↑ in dabigatran concentration	Atrial Fibrillation	**CrCl 30-50 mL/min:** 75 mg twice daily (dronedarone or systemic ketoconazole) **CrCl < 30 mL/min:** Avoid use
		Treatment of DVT/PE	**CrCl < 50 mL/min:** Avoid use
		Prophylaxis of DVT/PE (hip/knee replacement)	**CrCl < 50 mL/min:** Avoid use In patients with CrCl ≥50 mL/min who are concomitantly on a P-gp inhibitor, it may be helpful to separate the timing of administration by several hours.

Inducers of P-gp**	***Significant*** ↓ in dabigatran concentration	All indications	Avoid use

The use of the P-gp inhibitors verapamil, amiodarone, quinidine, clarithromycin, and ticagrelor does not require a dose adjustment of dabigatran in non-valvular atrial fibrillation if CrCl >30 mL/min. These results should not be extrapolated to other-gp inhibitors. When immediate-release verapamil is taken within 1 h prior to dabigatran intake, plasma levels of dabigatran may increase up to 180%. Separating both drugs' intake ≥2 h removes the interaction. With a slow-release verapamil preparation, there may be a 60% increase in dabigatran concentration.

EDOXABAN (SAVAYSA)			
DRUG CLASS	**TYPE OF INTERACTION**	**INDICATION**	**RECOMMENDATIONS**
Inhibitors of P-gp*	***Significant*** ↑ in edoxaban concentration	Atrial Fibrillation	No dose adjustment necessary
		Treatment of DVT/PE	**Reduce dose to 30 mg daily** (verapamil, quinidine, azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole)†
Inducers of P-gp**	***Significant*** ↓ in edoxaban concentration	All indications	**Rifampin**: Avoid use **All other agents:** No specific recommendations provided per manufacturer labeling. Avoid use if possible.

† Other P-gp inhibitors were not permitted in the Hokusai VTE study.

***Inhibitors of P-gp** *(list not exhaustive)*		****Inducers of P-gp** *(list not exhaustive)*
Amiodarone Azithromycin Carvedilol Clarithromycin Conivaptan Cyclosporine Diltiazem Dronedarone Erythromycin Grapefruit juice Itraconazole Ketoconazole Lapatinib Mefloquine	Nelfinavir Nicardipine Lopinavir/ritonavir Propafenone Quinidine Ranolazine Ritonavir Saquinavir Tacrolimus Tamoxifen Telaprevir Ticagrelor Verapamil	Rifampin Carbamazepine Phenytoin Phenobarbital St. John's wort

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with apixaban or rivaroxaban.

PATIENT EDUCATION INFORMATION

Patient Education Handouts (See also, individual documents in Epic under *IM* AMS-[DOAC name] Patient Education* and shorter documents available with the SmartLink *.C2DrugAll*):

- Apixaban (Eliquis): Apixaban (Eliquis)
- Rivaroxaban (Xarelto): Rivaroxaban (Xarelto)
- Dabigatran (Pradaxa): Dabigatran (Pradaxa)
- Edoxaban (Savaysa): Edoxaban (Savaysa)
- Betrixaban (Bevyxxa): Betrixaban (Bevyxxa)

Appearance of Tablets

Eliquis apixaban **5mg tab**	**Eliquis** apixaban **2.5mg tab**	**Xarelto** rivaroxaban **20mg tab**	**Xarelto** rivaroxaban **15mg tab**	**Xarelto** rivaroxaban **10mg tab**	**Xarelto** rivaroxaban **2.5 mg tab**	**Pradaxa** dabigatran **150mg cap**	**Pradaxa** dabigatran **110mg cap**	**Pradaxa** dabigatran **75mg cap**	**Savaysa** edoxaban **60mg tab**	**Savaysa** edoxaban **30mg tab**	**Savaysa** edoxaban **15mg tab**	**Bevyxxa** betrixaban **40 mg and 80 mg cap**
												

Alternative Administration:

Apixaban (Eliquis)	• 5 mg and 2.5 mg tablets may be crushed and suspended in water, 5% dextrose in water (D5W), or apple juice, or mixed with applesauce and promptly administered orally. Alternatively, ELIQUIS tablets may be crushed and suspended in 60 mL of water or D5W and promptly delivered through a nasogastric tube • Crushed tablets are stable in water, D5W, apple juice, and applesauce for up to 4 hours
Rivaroxaban (Xarelto)	• 10 mg, 15 mg or 20 mg tablets may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed 15 mg or 20 mg tablet, the dose should be immediately followed by food. • Administration via nasogastric (NG) tube or gastric feeding tube: After confirming gastric placement of the tube, 10 mg, 15 mg or 20 mg tablets may be crushed and suspended in 50 mL of water and administered via an NG tube or gastric feeding tube. Since rivaroxaban absorption is dependent on the site of drug release, avoid administration distal to the stomach which can result in reduced absorption and thereby, reduced drug exposure. After the administration of a crushed 15 mg or 20 mg tablet, the dose should then be immediately followed by enteral feeding. • Crushed 10 mg, 15 mg or 20 mg tablets are stable in water and in applesauce for up to 4 hours. An in vitro compatibility study indicated that there is no adsorption of rivaroxaban from a water suspension of a crushed XARELTO tablet to PVC or silicone nasogastric (NG) tubing.
Dabigatran (Pradaxa)	• Capsules should be swallowed whole and taken with a full glass of water. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure.
Edoxaban (Savaysa)	• Tablets may be crushed and mixed with 2 to 3 ounces of water and immediately administered by mouth or through a gastric tube. The crushed tablets may also be mixed into applesauce and immediately administered orally.

Storage:

- **Apixaban (Eliquis), rivaroxaban (Xarelto), and edoxaban (Savaysa):** Store at room temperature, but can be taken out of original container and stored in pillboxes, etc.
- **Dabigatran (Pradaxa)**: Store in the original package to protect from moisture and keep the bottle tightly closed. Once bottle is opened, the product must be used within 4 months. Capsules cannot be moved to pillboxes, etc. and should be stored in original bottle only.

Handling Dosing Errors:

Missed Dose	• General rule: A forgotten dose may be taken until 50% of the dosing interval has passed:
	  ○ For DOACs with a BID dosing regimen (i.e. every 12 h), a forgotten dose can be taken up until 6 h after the scheduled intake. For patients with a high thrombotic risk and low bleeding risk, this may be extended.
	  ▪ Specifically for patients taking acute VTE treatment dose of rivaroxaban (Xarelto) 15mg BID (total of 30mg in 1 day), patient can take dose as soon as remembered on the same day and may take 2 doses at the same time to make up for the missed dose. Next dose should be taken at regularly scheduled time.
	  ○ For DOACs with a once-daily dosing regimen, a forgotten dose can be taken up until 12 h after the scheduled intake. After this time point, the dose should be skipped and the next scheduled dose should be taken. The 12 h interval may be extended in patients with a high thrombotic risk.

Double Dose	• For DOACs with a BID dosing regimen, the next planned dose (i.e. after 12 h) may be left out, with BID intake restarted 24 h after the double dose intake. • For DOACs with a once-daily dosing regimen, the patient should continue the normal dosing regimen, i.e. without skipping the next daily dose.
Uncertainty About Dose Intake	• For DOACs with a BID dosing regimen, it is generally advisable to not take another tablet/capsule, but to simply continue with the regular dose regimen, i.e. starting with the next dose at the 12 h interval. • For DOACs with a once-daily dosing regimen, when thrombotic risk is high (e.g., CHA2DS2-VASc ≥3), it may generally be advisable to take another tablet and then continue the planned dose regimen. In case the thrombotic risk is low (e.g., CHA2DS2-VASc ≤2), it is recommended to wait until the next scheduled dose.

Recommendations adapted from the European Heart Rhythm Association Practical Guide on use of DOACs in patients with AF (2018)

SWITCHING DOACs FROM/TO WARFARIN AND OTHER ANTICOAGULANTS[66-69 above, 124-125]

<table>
<tr><th></th><th>EDOXABAN</th><th>APIXABAN</th><th>RIVAROXABAN</th><th>DABIGATRAN</th></tr>
<tr><td>Switching FROM warfarin</td><td>Discontinue warfarin and start when INR ≤2.5</td><td>Discontinue warfarin and start when INR <2.0</td><td>Discontinue warfarin and start when INR <3.0</td><td>Discontinue warfarin and start when INR <2.0</td></tr>
<tr><td>Switching TO warfarin
(Low to moderate short-term risk for thrombosis)</td><td colspan="3">Oral option: Start warfarin and stop DOAC 3 days later.
• Test trough INR ≥ 12h after last apixaban dose
• Test trough INR ≥ 24h after last edoxaban or rivaroxaban dose.

Alternative oral option: Stop DOAC and start warfarin</td><td>Oral option:
• CrCl ≥ 50 mL/min: start warfarin 3 days prior to stopping dabigatran.
• CrCL 30-50 mL/min: start warfarin 2 days prior to stopping dabigatran.
• CrCL 15-30 mL/min: start warfarin 1 day prior to stopping dabigatran.
• CrCL<15 mL/min: no recommendations provided. Refer to AMS consultant for clinical decision

Test INR ≥ 12 hours after last dabigatran dose.</td></tr>
<tr><td>Switching TO warfarin
(High short-term risk for thrombosis)

Transition should be deferred until after high risk period if possible</td><td>Oral option: If on edoxaban 60 mg, reduce dose to 30 mg and begin warfarin at that time. If on edoxaban 30 mg, reduce dose to 15 mg and begin warfarin at that time. Measure INR at least weekly, with test done just prior to the daily dose of edoxaban. Once a stable INR ≥2.0 achieved, discontinue edoxaban.

Parenteral option: Discontinue edoxaban and give a parenteral anticoagulant and warfarin at the time of next scheduled edoxaban dose. Discontinue parenteral anticoagulant once INR is therapeutic.</td><td colspan="3">Oral option: Start warfarin, and overlap DOAC and warfarin until INR in goal range (e.g., ≥2.0). Measure INR at trough DOAC level (right before the next dose) on 3rd day of concomitant use, then daily as needed until INR at trough DOAC level is within goal. Stop DOAC once INR is within goal' and then re-measure INR 24 hours after last DOAC dose to ensure adequate anticoagulation. Closely monitor INR during first month of therapy to ensure stability (i.e., 3 consecutive INRs in range).

Parenteral option: Discontinue DOAC and give a parenteral anticoagulant and warfarin at the time of next scheduled DOAC dose. Discontinue parenteral anticoagulant once INR is therapeutic.</td></tr>
</table>

[124] Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015 Aug 31.

[125] Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis. 2016; 41(1):206-32.

Switching FROM/TO other DOACs	Stop current DOAC and begin new DOAC at next scheduled dose. In situations where higher than therapeutic range of DOAC expected (e.g., compromised renal function), consider delaying initiation of new DOAC. Check renal function and ensure proper dosing before starting new DOAC.	
Switching FROM LMWH	DOACs can be initiated when the next dose of LMWH would have been given.	
Switching TO LMWH	LMWH can be initiated when the next dose of apixaban, rivaroxaban, or edoxaban would have been given.	**For CrCl ≥30 mL/min**: Start LMWH 12 hours after the last dose of dabigatran **For CrCl < 30 mL/min**: Start LMWH 24 hours after the last dose of dabigatran
Switching FROM UFH	IV: DOAC can be initiated at the time IV UFH is discontinued. Care should be taken in patients with CKD where the elimination of heparin may take longer. SQ: DOAC can be initiated approximately 4–5 h after the last dose of SC UFH.	
Switching TO UFH	UFH can be initiated when the next dose of apixaban, rivaroxaban, or edoxaban would have been given.	**For CrCl ≥30 mL/min**: Start UFH 12 hours after the last dose of dabigatran **For CrCl < 30 mL/min**: Start UFH 24 hours after the last dose of dabigatran

Appendix 11: Considerations for Anticoagulant Selection in Atrial Fibrillation and VTE Treatment

ANTICOAGULANT SELECTION BASED ON PATIENT CHARACTERISTICS:

Step 1: **Establish diagnosis and decision for medical treatment**:

VTE:

- Patients with objectively confirmed DVT or PE without evidence of respiratory compromise or hemodynamic instability can usually be treated in the outpatient setting.

Non-valvular atrial fibrillation:

- Diagnosis of non-valvular atrial fibrillation or atrial flutter (documented by Holter monitor, event monitor or electrocardiogram) in the absence of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or a mechanical heart valve.
- Decision needs to be made that an oral anticoagulant (DOAC or warfarin) vs. (aspirin or no therapy) is needed)

Valvular atrial fibrillation:

- Atrial fibrillation or flutter in the setting of moderate-to-severe mitral stenosis (potentially requiring surgical intervention) or in the presence of a mechanical heart valve. This definition matches other contemporary guidelines.
- Warfarin remains recommended option in this setting (AHA/ACC/HRS-2019).

2018 European Heart Rhythm Association Suggestions on Valvular Indications and Contraindications for DOAC Therapy[126]:

CONDITION	ELIGIBILITY FOR DOAC THERAPY
Mechanical prosthetic valve	**Contraindicated**
Moderate to severe mitral stenosis (usually of rheumatic origin)	**Contraindicated**
Mild to moderate other native valvular disease (e.g., mild-aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	**Included in DOAC trials**
Severe aortic stenosis	**Limited data (excluded in RE-LY)** **Most will undergo intervention**
Bioprosthetic valve (after > 3 months post-operatively)*	**Not advised if for rheumatic mitral stenosis**
	Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post-operatively)*	**Some patients included in DOAC trials**
Percutaneous transluminal aortic valvuloplasty (PTAV) and transcatheter aortic valve implantation (TAVI)	**No prospective data yet** **May require combination with single or dual antiplatelet therapy**
Hypertrophic cardiomyopathy	**Limited data, but patients may be eligible for DOACs**

Note: hatched pattern = limited data

* American guidelines have not yet clearly supported use of DOACs in patients with bioprosthetic heart valves or after valve repair. Note that the phase 3 GALILEO trial was terminated early after a preliminary analysis showed that rivaroxaban (Xarelto) was associated with an increase in all-cause death, thromboembolic events, and bleeding when given following successful transcatheter aortic valve replacement (TAVR).

Step 2: **Choose best drug for patient (see table below for general guidance)**

- Note that all DOACs have substantially higher copays than warfarin, and thus higher cost to patients in most insurances. The decision to place patients on a DOAC depends on the balance between the patient's risk factors, lifestyle issues, insurance coverage, and ability to sustain higher copays. Decisions must include assessment of the underlying condition and patient preferences and resources, as well as potential complications of each management option. **Also, to achieve the favorable results of studies comparing DOACs to warfarin, clinicians must monitor patient adherence and ensure that changes in renal function or prescribed medications do not decrease the efficacy or increase the risks of these drugs. In addition, it is essential to ensure that gaps in insurance coverage do not result in patient non-compliance.**

ANTICOAGULATION SELECTION BASED UPON PATIENT CHARACTERISTICS:

[126] The 2018 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Eur Heart J 2018;Mar 19

PATIENT CHARACTERISTIC	DRUG TO CONSIDER	RATIONALE/COMMENTS
Prosthetic Heart Valves	**warfarin**	Mechanical prosthetic heart valves: dabigatran inferior to warfarin in patients with mechanical prosthetic heart valves and contraindicated in this group; other DOACs not studied in this patient population and are not recommended. Bioprosthetic heart valves: the evidence of using DOACs in patients with bioprosthetic heart valves is limited, however both U.S. and European guidelines consider these patients possibly eligible for DOAC therapy assuming absence of rheumatic mitral stenosis and after >3 months postoperatively (per European Heart Rhythm Association). Based on the GALILEO study[127], which found patients undergoing TAVR without AF at baseline randomized to rivaroxaban experienced higher rates of death and bleeding compared to those randomized to an anti-platelet regimen, U.S. labeling advises against use of rivaroxaban in patients who have had a TAVR. Studies evaluating apixaban[128] and edoxaban[129] in patients with AF undergoing TAVR are ongoing.
Moderate to severe mitral stenosis	**warfarin**	Presence of significant valvular disease was excluded from DOAC clinical trials. U.S. and European guidelines advise against DOAC use in this setting.
Moderate to severe hepatic impairment (Child-Pugh B and C) or liver disease with coagulopathy	**warfarin or LMWH** *Note: warfarin may be difficult to control and INR may not reflect antithrombotic effect.*	Rivaroxaban: not recommended in moderate-severe hepatic impairment or any hepatic disease associated with coagulopathy. Edoxaban: not recommended in moderate-severe hepatic impairment. Apixaban: not recommended in severe hepatic impairment. Specific dosing recommendations in moderate impairment cannot be provided. Dabigatran: dabigatran in patients with moderate hepatic impairment showed a large inter-subject variability. Patients with active liver disease were excluded from clinical trials.
CrCl <15 mL/min	**warfarin or apixaban**	CrCl <30 mL/min excluded from rivaroxaban, dabigatran, and edoxaban pivotal clinical trials. • Rivaroxaban labeling does not recommend use for VTE indications when CrCl is <15 mL/min • Dabigatran labeling does not recommend use for VTE indications when CrCl <30 mL/min or for NVAF when CrCl is < 15 mL/min • Edoxaban labeling does not recommend use when CrCl is <15 mL/min CrCl <25mL/min or Scr >2.5mg excluded from apixaban clinical pivotal trials, though U.S. labeling allows for use in ESRD for all approved indications. The 2019 AHA/ACC/HRS afib guideline[Error! Bookmark not defined.] recommends against use of dabigatran, rivaroxaban, or edoxaban in ESRD, but warfarin or apixaban are considered reasonable options if anticoagulation is indicated.

[127] Dangas GD, Tijssen JGP, Wöhrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382(2):120-129.
[128] Collet JP, Berti S, Cequier A, et al. Oral anti-xa anticoagulation after trans-aortic valve implantation for aortic stenosis: The randomized ATLANTIS trial. *Am Heart J*. 2018;200:44-50.
[129] Van Mieghem NM, Unverdorben M, Valgimigli M, et al. Edoxaban versus standard of care and their effects on clinical outcomes in patients having undergone transcatheter aortic valve implantation in atrial fibrillation-rationale and design of the ENVISAGE-TAVI AF trial. *Am Heart J*. 2018;205:63-69.

PATIENT CHARACTERISTIC	DRUG TO CONSIDER	RATIONALE/COMMENTS
		If a DOAC is used in CrCl 15-30mL/min, proper dose adjustment should be made per agent and indication (see indication chart below).
Stroke prevention in NVAF with CrCl > 95 mL/min (per Cockcroft-Gault)	**warfarin, apixaban, or rivaroxaban**	Edoxaban inferior to warfarin in these patients and therefore should not be used in these patients. Dabigatran can be used if CrCl >95mL/min, but is non-formulary.
Requirement for compliance aid such as pill box	**warfarin, apixaban, or rivaroxaban**	Dabigatran capsules must be kept in original container. Although edoxaban can be stored in pillboxes, it is non-formulary.
Once daily oral therapy preferred	**warfarin or rivaroxaban**	Apixaban and dabigatran require BID dosing. Note: rivaroxaban requires BID dosing for initial 21 days of VTE treatment. Although dosed once daily, edoxaban is non-formulary.
Difficulty swallowing/need for alternative administration	**warfarin, apixaban, or rivaroxaban**	Warfarin: tabs can be crushed Apixaban: tabs may be crushed and suspended in water, D5W, or apple juice, or mixed with applesauce and promptly administered (stable up to 4 hrs). Alternatively, tabs may be crushed and suspended in 60mL of water or D5W and promptly delivered through a nasogastric tube. Rivaroxaban: tabs may be crushed and mixed with applesauce and immediately administered (stable up to 4 hrs). 15mg or 20mg dose should be immediately followed by food. Alternatively, tabs may be crushed and suspended in 50mL of water and administered via an NG tube or gastric feeding tube. Avoid administration distal to the stomach. After 15mg or 20mg dose, immediately follow with enteral feeding. Dabigatran: swallow caps whole- do not open or crush. Edoxaban (non-formulary): tabs may be crushed and mixed with 2-3 ounces of water and immediately administered by mouth or through a gastric tube. Crushed tabs may also be mixed into applesauce and immediately administered orally.
Dyspepsia or gastrointestinal (GI) bleed history	**warfarin or apixaban**	Dabigatran commonly causes dyspepsia. Dabigatran, rivaroxaban and edoxaban may be associated with more GI bleeding than warfarin.
VTE, parenteral drug avoidance	**apixaban or rivaroxaban**	Warfarin, dabigatran and edoxaban require initial parenteral therapy.
Pregnancy or pregnancy risk	**LMWH**	Potential for other agents to cross the placenta. LMWH generally agent of choice in pregnancy.
Breast feeding	**LMWH or warfarin**	It is unknown if DOACs are excreted in breast milk. Warfarin and LMWH generally considered compatible with breastfeeding.

PATIENT CHARACTERISTIC	DRUG TO CONSIDER	RATIONALE/COMMENTS
VTE without active cancer	**apixaban, rivaroxaban or warfarin**	The 2016 CHEST guidelines for VTE treatment for patients without cancer recommend DOACs as preferred therapy over enoxaparin + warfarin due to similar efficacy and lower risk of bleeding, specifically intracranial hemorrhage, as well as greater convenience for patients and clinicians.[130] The 2017[131] and 2019[132] European Society of Cardiology (ESC) guidelines for management of VTE recommend DOACs as the first choice for anticoagulation treatment in a patient eligible for DOACs; VKAs are an alternative to DOACs. Therefore, formulary DOACs **apixaban (Eliquis)** or **rivaroxaban (Xarelto)** **are considered 1st line agents for outpatient management of non-cancer DVT and low-risk PE** with **enoxaparin + warfarin** as a preferred alternative for patients inappropriate for DOACs. **Drug choice should be based on careful consideration of patient characteristics.**
VTE with active cancer	**apixaban, rivaroxaban, LMWH, or warfarin (DOAC or LMWH preferred over warfarin)**	The 2016 CHEST guidelines for VTE treatment for patients with cancer recommend LMWH as preferred therapy over warfarin or DOACs. Recommendation for LMWH is stronger if: VTE was just diagnosed, extensive, metastatic cancer, very symptomatic; vomiting; on chemotherapy.[133] Since publication of the 2016 CHEST guidelines, rivaroxaban, apixaban, and edoxaban have been evaluated vs dalteparin in small randomized open-label trials in cancer patients with acute VTE. Rivaroxaban and edoxaban demonstrated lower rates of recurrent VTE, but higher rates of bleeding (rivaroxaban: SELECT-D trial[134]; edoxaban: Hokusai VTE Cancer trial[135]). Apixaban demonstrated lower rates of recurrent VTE with similar bleeding (ADAM VTE trial[136]). 2018 International Initiative on Thrombosis and Cancer (ISTH) Guidance[137], the 2019 American Society of Clinical Oncology Guideline[138], and the 2019 International Initiative on Thrombosis and Cancer (ITAC) Guideline[139] (all published prior to publication of ADAM VTE evaluating

[130] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. *Chest*. 2016;149(2):315-352.

[131] Diagnosis and management of acute deep vein thrombosis: a joint consensus document from the European Society of Cardiology working groups of aorta and peripheral vascular diseases and pulmonary circulation and right ventricular function; European Heart Journal, Volume 39, Issue 47, 14 December 2018, Pages 4208–4218

[132] 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC): European Heart Journal, Volume 41, Issue 4, 21 January 2020, Pages 543–603

[133] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. *Chest*. 2016;149(2):315-352.

[134] Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: Results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017-2023.

[135] Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378(7):615-624.

[136] McBane RD,2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. *J Thromb Haemost*. 2020;18(2):411-421

[137] Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: Guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16(9):1891-1894.

[138] Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *JCO*. 2020;38(5):496-520.

[139] Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2019;20(10):e566-e581.

PATIENT CHARACTERISTIC	DRUG TO CONSIDER	RATIONALE/COMMENTS
		apixaban) generally recommend use of LMWH or specific DOACs (rivaroxaban or edoxaban based on evidence at time of publication) as preferred therapies for VTE treatment in cancer patients. In setting of low bleeding risk and no-drug-drug interactions, DOACs may be preferred, while LMWH may be preferred in the setting of high risk of bleeding (including luminal GI cancers with an intact primary, cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or active GI mucosal abnormalities (duodenal ulcers, gastritis, esophagitis, or colitis)). Therefore, formulary DOACs, **apixaban (Eliquis)** or **rivaroxaban (Xarelto)**, or **enoxaparin** are considered 1st line agents for VTE treatment in cancer. Edoxaban (Savaysa) also has evidence in this setting, but is non-formulary and requires initial parenteral therapy. In the setting of high risk of bleeding, such as GI tract malignancies, **enoxaparin** may be preferred. **Shared-decision making incorporating patient preferences and values is required.**
VTE in presence of coronary artery disease	**warfarin, apixaban, or rivaroxaban**	Coronary events appear to occur more often with dabigatran than with warfarin. This has not been seen with the other DOACs. Antiplatelet therapy should be avoided if possible in setting of anticoagulation due to increased bleeding. Although coronary artery events did not appear to occur more often with edoxaban vs. warfarin, edoxaban is non-formulary.
Poor adherence	**warfarin**	INR monitoring can help to detect problems. Switching to a shorter half-life DOAC in patients who frequently miss warfarin doses may more rapidly predispose them to risk of thrombosis. However, some patients may be more compliant with a DOAC because it is less complex and in these patients, a DOAC can be considered.
Reversal agent may be needed	**Warfarin, unfractionated heparin, apixaban, or rivaroxaban** Alternative: enoxaparin	Protamine is a partial reversal agent for enoxaparin. Reversal agent (Andexxa) for apixaban and rivaroxaban is available. Andexxa is not currently approved for reversal of edoxaban or other FXa inhibitors. Dabigatran has approved reversal agent (Praxbind), but is non-formulary. No reversal agent available for fondaparinux.
Extremes of weight (<50kg or >120kg) or BMI >40 kg/m^2	**warfarin**	Patients at extreme weights represented a small proportion of the patients in DOAC trials. Pending further evidence in patients at extreme weights, it is advisable to limit DOAC use to situations where warfarin can't be used. If a DOAC is used, AMS recommends shared decision making between patient and clinician.
History of bariatric surgery or significant bowel resection	**warfarin**	Warfarin is generally recommended in this population, as it can be monitored with the INR and dose-adjusted. Published data describing DOAC absorption, pharmacokinetics/pharmacodynamics, and clinical efficacy and safety are too sparse to support routine use of DOACs in this setting. Exceptions may include partial resection of the colon (e.g., left or right hemicolecetomy or sigmoid colectomy) or patients with a colostomy as there should be little impact on medications absorptive capacity.

PATIENT CHARACTERISTIC	DRUG TO CONSIDER	RATIONALE/COMMENTS
Antiphospholipid Syndrome (APS)	**warfarin**	There have been several studies[140] that indicate an increased thrombotic rate in patients with APS taking DOACs vs. warfarin, prompting an official warning in the labeling of DOACs. DOACs are "not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy."[141]
Difficulty affording medications	**warfarin**	All DOACs will generally be a higher copay tier for patients and will have significantly higher out-of-pocket cash price.

Appendix 12: Antiplatelet Therapy and Warfarin Drug-Drug Interactions

Both anticoagulants and antiplatelet agents increase the risk of bleeding, including minor, major, and life-threatening bleeding. When oral anticoagulation (OAC) is combined with low dose ASA, this risk increases, and is commonly designated as approximately twice the bleeding risk of warfarin (or DOACs) alone. When patients on lifelong OAC are taking dual antiplatelet therapy, such as following acute coronary syndrome (ACS) if already on ASA, coronary artery bypass graft (CABG), or placement of a coronary artery stent, the risk of bleeding increases even more. See Appendix 1 for indications of lifelong OAC. From various studies, the bleeding risks of OAC alone or in combination anticoagulant/antiplatelet therapy is unavoidable and the benefit clearly exceeds the risk. In these situations, the other factors determining the patient's bleeding risk play a major role, so a patient with a low baseline bleeding risk might have a recommendation for treatment more aggressive than a patient with a high baseline bleeding risk. These situations occur most commonly during the first twelve months of treatment for acute ischemic events such as occurrence of ACS, CABG, or stent placement.

In atrial fibrillation patients in which aspirin is concomitantly used with warfarin or DOAC, we suggest a dose of 75-100 mg daily with concomitant use of PPI to minimize upper gastrointestinal bleeding.

From various studies, the risks of single and dual antiplatelet/anticoagulant treatment include:

Treatment	Yearly risk of major bleeding
Warfarin alone	• Age <60: 1.5 • Age 60 to 70: 2.1 • Age 71 to 80: 2.5 • Age >80: 4.2[142]
DOACs alone	• Apixaban: rate of major bleeding in apixaban group was 2.13% per year vs. 3.09% per year in the warfarin group[143]

[140] Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome; Blood. 2018 Sep 27;132(13):1365-1371

[141] Eliquis Package Insert

[142] Weiloch, M, et al; Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thromboembolic complications from the national quality registry AuriculA; Eur Heart J (2011) 32 (18): 2282-2289

[143] Hylek, EM, et al; Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin - The ARISTOTLE trial; Journal of the American College of Cardiology; Vol 63, Issue 20, May 2014

	• Rivaroxaban: rate of major bleeding in rivaroxaban group was 3.6% per year vs. 3.5% per year in the warfarin group major[144] • Dabigatran: rate of major bleeding in dabigatran group was 3.47% per year vs. 3.58% per year in the warfarin group[145] • Edoxaban: rate of major bleeding in edoxaban group was 3.1% per year vs. 3.7% per year in the warfarin group[146]
Warfarin + ASA	Combined therapy confers a 1-2% absolute risk increase in major (serious) bleeding per year compared with warfarin alone[147]
DOAC + ASA	Apixaban: rate of major bleeding of patients on ASA at randomization + apixaban was 2.7% per year vs. 1.9% per year in patients on apixaban only[88] Rivaroxaban: rate of major bleeding of patients on ASA at randomization + rivaroxaban was 4.5% per year vs. 3.1% per year in patients on rivaroxaban only[89] Dabigatran: rate of major bleeding of patients on ASA at randomization + dabigatran was 4.12% per year vs. 3.08% per year in patients on dabigatran only[90] Edoxaban: rate of major bleeding of patients on ASA at randomization + edoxaban was 3.50% per year vs. 2.35% per year in patients on edoxaban only[91]
Warfarin + dual antiplatelets	Using warfarin monotherapy as a reference, the hazard ratio (95% confidence interval) for the combined end point was 0.93 (0.88-0.98) for aspirin, 1.06 (0.87-1.29) for clopidogrel, 1.66 (1.34-2.04) for aspirin-clopidogrel, 1.83 (1.72-1.96) for warfarin-aspirin, 3.08 (2.32-3.91) for warfarin-clopidogrel, and 3.70 (2.89-4.76) for warfarin-aspirin-clopidogrel[148]

In the presence of an anticoagulant for AF, prosthetic heart valve, or other valid indication for anticoagulant, the accepted indications for the addition of an antiplatelet agent include:

- Acute ischemic cardiac syndrome, especially if acute
- Presence of CABG, especially if acute
- Presence of a coronary artery stent, especially if acute
- Presence of a mechanical heart valve, with or without atrial fibrillation
- Stroke/TIA while on an anticoagulant in therapeutic range (e.g. anticoagulant failure), especially if acute, i.e. within initial 6 months after occurrence
- Intractable peripheral artery disease.

Additionally, the presence of stable coronary artery disease in a patient requiring anticoagulation (for example, due to atrial fibrillation or VTE) may be a reasonable indication for dual therapy in patients at high risk of coronary events and low risk of bleeding. There is little evidence to support or refute this indication, so it remains controversial.

There are no circumstances when antiplatelets should be added to an anticoagulant for primary prevention of cardiovascular disease. Regardless of the cardiovascular risk score, which is calculated based on a 10-year risk, the combined yearly risk of bleeding from combined anticoagulant/antiplatelet agents, carried over 10-years, will virtually always be higher.

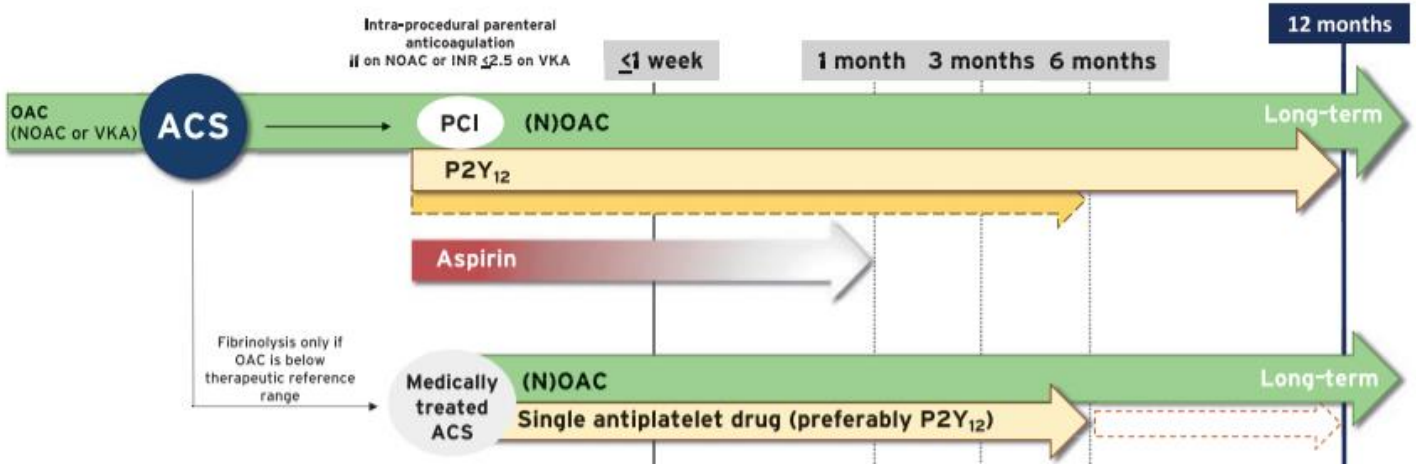
[145] Xarelto Prescribing Information, Janssen Pharmaceuticals, Inc. 2017
[145] Pradaxa Prescribing Information, Boehringer Ingelheim Pharmaceuticals, Inc. 2018
[146] Savaysa Prescribing Information, Daiichi Sankyo Co., LTD, 2017
[147] Douketis, JD; Combination warfarin-ASA therapy: Which patients should receive it, which patients should not, and why?; Thrombosis Research 127 (2011) 513–517
[148] Hansen, ML et al; Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation; Arch Intern Med. 2010;170(16):1433-1441. doi:10.1001/archinternmed.2010.271

Below are summaries of the current guidelines (2016 ACA/AHA and 2020 European Society of Cardiology) regarding use of combination oral anticoagulants and antiplatelet agents, followed by recommendations from consideration of additional interim publications and from Atrius Cardiology consultations.

Summary and Synthesis of Recommendations on the Management of Patients Treated With Triple Therapy per the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease[149]:

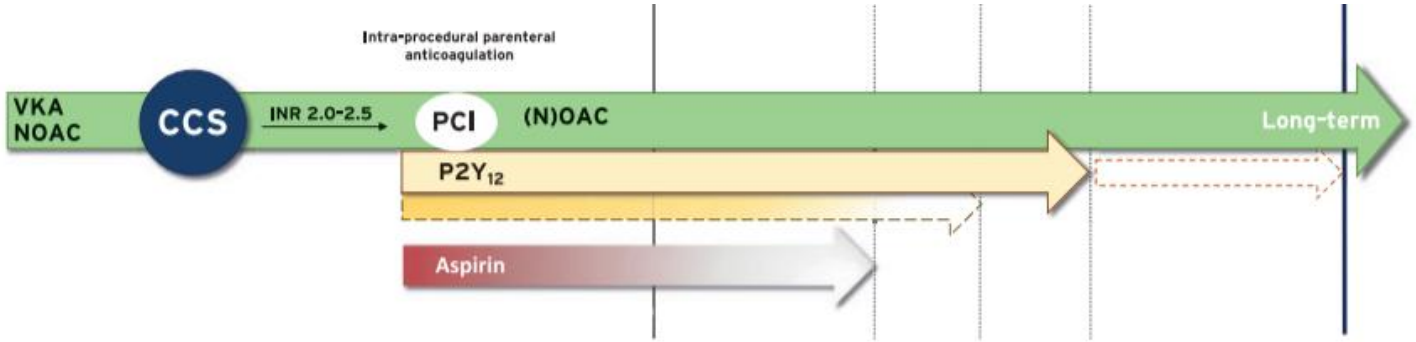
- Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA2DS2-VASc, HAS-BLED)
- Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients

2020 European Society of Cardiology (ESC) Recommendations for Combination Therapy with Oral Anticoagulants and Antiplatelets in patients with AF[150]:



[149] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. Circulation. 2016 Lippincott Williams & Wilkins; 134(10):e123-55.

[150] Hindricks G, Potpara T, Dagres N, et al 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498.



ACS= acute coronary syndrome; AF= atrial fibrillation; CCS= chronic coronary syndrome; OAC= oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI= percutaneous coronary intervention; VKA= vitamin K antagonist. Full-outlined arrows represent a default strategy; graded/dashed arrows show treatment modifications depending on individual patient's ischemic and bleeding risks.

Based on these considerations, the following is recommended:

Acute CAD: The initial 12 month timeframe after occurrence of ACS, CABG, or stent placement is considered the highest risk time for thrombotic events and is considered a valid reason to add single and/or dual antiplatelet therapy with ASA 75-100mg and/or P2Y12 receptor blocker to an oral anticoagulant (OAC), regardless of the indication for the OAC.

Stable CAD: Long term management, following completion of 12 months of initial treatment, is based on thrombotic vs bleeding risk (**see** Appendix 5 **for bleeding risk score**). Valid reasons to withdraw single and/or dual antiplatelet therapy include:

- **Patients with ACS who have completed at least 12 months of low dose aspirin and/or P2Y12 inhibitor:** if asymptomatic throughout treatment, at very high bleeding risk vs clotting risk, and if no indications for revascularization procedure, **OAC alone can be used in consultation with treating cardiologist.**
- **Patients with CABG without complicated anatomy who have completed at least 12 months of low dose aspirin and/or P2Y inhibitor**: if asymptomatic throughout treatment and at very high bleeding risk vs clotting risk**, OAC alone can be used in consultation with treating cardiologist.**
- **Patients with stent placement but without history of previous stent, complicated stent placement, or BMS, who have completed at least 12 months of low dose aspirin and P2Y12 inhibitor:** if asymptomatic throughout treatment and at very high bleeding risk vs clotting risk, **OAC alone can be used in consultation with treating cardiologist.**

- There remains limited further evidence to strongly support use of OAC alone, with one study unable to demonstrate non-inferiority of various oral anticoagulant treatments, most commonly DOACs, compared to dual antiplatelet/anticoagulant therapy[151] and another study demonstrating non-inferiority of monotherapy with rivaroxaban compared to dual antiplatelet therapy in patients with stable CAD > 12 months after PCI.[152]

PPI use in the presence of dual anticoagulant/antiplatelet therapy: There are no controlled clinical trials to demonstrate the efficacy of proton pump inhibitors in decreasing bleeding events of patients on anticoagulation. However, antiplatelet agents all carry the risk of gastric ulceration, as well as direct increase in risk of bleeding from the antiplatelet effects. Given the inherent risk of GI bleeding with warfarin, increased in the presence of antiplatelet agents, and the ability of PPIs to decrease the likelihood of gastric ulcers, it is prudent to use PPIs when warfarin and antiplatelet agents are required as dual therapy.

Other Medications with Antiplatelet Effects

- Non-antiplatelet medications such as NSAIDs[153] and selective serotonin reuptake inhibitors (SSRIs)[154] have been shown to have a degree of antiplatelet effect, a mechanism that likely contributes to the increased risk of bleeding that is seen when used in addition to anticoagulation therapy. This increase in bleeding is typically not accompanied by increases in INR due to the platelet-based mechanism. NSAIDs and SSRIs should be used with caution in patients on anticoagulation, especially for patients with a history of major bleeding.
- Although omega 3 fatty acids are thought to have similar antiplatelet effects, currently available data indicate no significant changes in time in therapeutic range for warfarin or incidence of bleeding[155], even when taken during or immediately after surgery.[156]

Treatment	Bleeding Risk (Given as Odds Ratios)
NSAIDs	**Warfarin (Non-Selective NSAIDs)** • Any bleeding (major + CRNMB): ~1.6[157] • Major bleeding: ~3.1 (8.4 per 100 patient years vs. 2.7)[158] • GI bleed: 1.9 to 2.0[19,159] • Clinically relevant non-major bleeding (CRNMB): ~2.1 (37.3 per 100 patient years vs. 17.4)[20] **Warfarin (COX-2 Selective NSAIDs)**

[151] Matsumura-Nakano et al; Open-Label Randomized Trial Comparing Oral Anticoagulation With and Without Single Antiplatelet Therapy in Patients With Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation; Circulation 2019: 139:604

[152] Yasuda, S et al; Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease: N Engl J Med 2019; 381:1103-1113

[153] Driver B, Marks DC, van der Wal DE. Not All (N)SAID and done: Effects of nonsteroidal anti-inflammatory drugs and paracetamol intake on platelets. *Res Pract Thromb Haemost*. 2020;4(1):36-45.

[154] Juurlink D. Antidepressants, antiplatelets and bleeding: One more thing to worry about? *CMAJ*. 2011;183(16):1819-1820.

[155] Pryce R, Bernaitis N, Davey A, et al. The Use of Fish Oil with Warfarin Does Not Significantly Affect either the International Normalised Ratio or Incidence of Adverse Events in Patients with Atrial Fibrillation and Deep Vein Thrombosis: A Retrospective Study. *Nutrients*. 2016;8(9):578.

[156] Begtrup KM, Krag AE, Hvas AM. No impact of fish oil supplements on bleeding risk: a systemic review. *Dan Med J.* 2017:64(5):A5366.

[157] Zapata LV, Hansten PD, Panic J, et al. Risk of Bleeding with Exposure to Warfarin and Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review and Meta-Analysis. *Thromb Haemost*. 2020;120(7):1066-1074.

[158] Davidson BL, Verheijen S, Lensing AWA et al. Bleeding Risk of Patients With Acute Venous Thromboembolism Taking Nonsteroidal Anti-Inflammatory Drugs or Aspirin. *JAMA Intern Med*. 2014;174(6):947-953.

[159] Battistella M, Mamdami M, Juurlink D, et al. Risk of Upper Gastrointestinal Hemorrhage in Warfarin Users Treated With Nonselective NSAIDs or COX-2 Inhibitors. *Arch Intern Med*. 2005;165(2):189-192.

	• Any bleeding (major + CRNMB): ~1.5[19] • GI Bleed: 1.7 to 2.5[19,21] **DOACs (All NSAIDs)** • Apixaban – NSAID effect on major bleeding, CRNMB, and GI bleeding is unclear[160] • Rivaroxaban – increases in major bleeding (~3.4, 4.7 per 100 patient years) and CRNMB (~2.4, 37.6 per 100 patient years)[20] • Dabigatran – increases in annual incidence of any bleeding (~1.5, 22.8% vs. 15.7%), major bleeding (~1.3, 4.4% vs. 3.3%), and GI bleeding (~1.5, 2.2% vs. 1.5%)[161]
SSRIs	**Warfarin**: • Major bleeding: ~1.7 (2.32 per 100 patient years vs. 1.35)[162] • Major bleeding (adjusted for bleeding risk and time spent with INR > 3.0): ~1.4 • 30 Day Mortality Rate After ICH: 2.10[163] Limited data regarding use of SSRIs and DOACs. A sub-group analysis of the ROCKET-AF trial showed no difference in any bleeding or major bleeding for rivaroxaban patients on SSRIs.[164]

Warfarin Drug-Drug Interactions

- The majority of warfarin drug-drug interactions involve modulation of the CYP450 enzyme system, which is responsible for metabolism of both enantiomers of warfarin (S-warfarin, R-warfarin). S-warfarin is metabolized primarily by CYP2C9 and R-warfarin is metabolized primarily by CYP3A4, 1A2, and 2C19.
- Drug-drug interactions that impact CYP2C9 result in the most profound impact on the INR as the anticoagulant effect produced by S-warfarin is approximately 2 to 5 times greater than R-warfarin.[165] Interactions that impact metabolism of S-warfarin will also be reflected in the INR more quickly given its shorter half-life compared to S-warfarin (21 to 43 hours vs. 37 to 89 hours).[166]

[160] Dalgaard F, Mulder H, Wojdyla DM, et al. Patients With Atrial Fibrillation Taking Nonsteroidal Anti-Inflammatory Drugs and Oral Anticoagulants in the ARISTOTLE Trial. *Circulation*. 2020;141:10-20.
[161] Kent AP, Brueckmann M, Fraessdorf M, et al. Concomitant Oral Anticoagulant and Nonsteroidal Anti-Inflammatory Drug Therapy in Patients With Atrial Fibrillation. *J Am Coll Cardiol*. 2018;72(3):255-267.
[162] Quinn GR, Singer DE, Chang Y, et al. Effect of Selective Serotonin Reuptake Inhibitors on Bleeding Risk in Patients with Atrial Fibrillation Taking Warfarin. *Am J Cardiol*. 2014;144(4):583-586.
[163] Lopponen P, Tetri S, Juvela S, et al. Association between warfarin combined with serotonin-modulating antidepressants and increased case fatality in primary intracerebral hemorrhage: a population-based study. *Journal of Neurosurgery JNS*. 2014;120(6):1358-1363.
[164] Quinn G, Hellkamp AS, Hankey GJ, et al. Selective Serotonin Reuptake Inhibitors and Bleeding Risk in Anticoagulated Patients With Atrial Fibrillation: An Analysis From the ROCKET AF Trial. *J Am Heart Assoc*. 2018;7(15):e008755.
[165] Minno AD, Frigerio B, Sadarella G, et al. Old and new oral anticoagulants: Food, herbal medicines and drug interactions. *Blood Rev*. 2017;31(4):193-203.
[166] Coumadin Prescribing Information, Bristol-Myers Squibb Co., 2019.

- Generally the onset and offset of CYP inhibition will reflect in the INR within 2 to 4 days of starting or stopping the interacting medication.[167] CYP inducers have a longer onset of action (1 to 3 weeks) and their effects can persist up to 5 weeks after discontinuing therapy.[168]

Mechanism of Interaction (CYP Pathway)*	Empiric Warfarin Dose Adjustment (% of weekly dose)[30]
Substrates	
3A4 (e.g., simvastatin, tramadol)	0 to 9% reduction[169]
1A2 (e.g., tizanidine)	None
2C9 (e.g., celecoxib)	0 to 15% reduction[29]
Inhibitors	
3A4 (e.g., itraconazole, ketoconazole, erythromycin, saquinavir, clarithromycin)	10% to 30% reduction[170]
1A2 (e.g., ciprofloxacin, levofloxacin, moxifloxacin)	0 to 25% reduction[171,172,173,174,175]
2C9 & 3A4 (e.g., amiodarone, fluconazole, metronidazole, sulfamethoxazole, voriconazole)	25% to 40% reduction[176,177,178,179,180,181]
Inducers	
2C9, 3A4, and 1A2 (e.g., carbamazepine, bosentan, phenobarbital, phenytoin, rifampin, ritonavir)	50% to 100% increase[182,183,184,185,186,187,188]

[167] Horn JR, Hansten, PD. Drug Interaction Mechanisms: Inhibition of CYP450 Metabolism. *Pharmacy Times*. 2016;82(6).
[168] Bungard TJ, Yakiwchuk E, Foisy, et al. Drug Interactions Involving Warfarin: Practice Tool and Practical Management Tips. *Canadian Pharmacists Journal*. 2011:144(1):21-25.
[169] Andersson ML, Mannheimer B, Lindh JD. The effect of simvastatin on warfarin anticoagulation: a Swedish register-based nationwide cohort study. *Eur J Clin Pharmcol*. 2019;75(10):1387-1392.
[170] Dandekar SS, Laidlaw DAH. Suprachoroidal haemorrhage after addition of clarithromycin to warfarin. *J R Soc Med* 2001;94:583-4.
[171] Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med* 2005;165:1095-106.
[172] Ellis RJ, Mayo MS, Bodensteiner DM. Ciprofloxacin–warfarin coagulopathy: a case series. *Am J Hematol* 2000;63:28-31.
[173] Ravnan SL, Locke C. Levofloxacin and warfarin interaction. *Pharmacotherapy* 2001;21:884-5.
[174] Carroll DN, Carroll DG. Interactions between warfarin and three commonly prescribed fluoroquinolones. *Ann Pharmacother* 2008;42:680-5.
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[180] Cook DE, Ponte CD. Suspected trimethoprim/sulfamethoxazole-induced hypoprothrombinemia. *J Fam Pract* 1994;39:589-91.
[181] Ahmed A, Stephens JC, Kaus CA, Fay WP. Impact of preemptive warfarin dose reduction on anticoagulation after initiation of trimethoprim–sulfamethoxazole or levofloxacin. *J Thromb Thrombolysis* 2008;26:44-8.
[182] Parrish RH, Pazdur DE, O'Donnell PJ. Effect of carbamazepine initiation and discontinuation on antithrombotic control in a patient receiving warfarin: case report and review of the literature. *Pharmacotherapy* 2006;26:1650-3.
[183] Lee CR, Thrasher KA. Difficulties in anticoagulation management during coadministration of warfarin and rifampin. *Pharmacotherapy* 2001;21:1240-6.
[184] Liedtke MD, Rathbun RC. Drug interactions with antiretrovirals and warfarin. *Expert Opin Drug Saf* 2010;9:215-23.
[185] Gatti G, Alessandrini A, Camera M, et al. Influence of indinavir and ritonavir on warfarin anticoagulant activity. *AIDS* 1998;12:825-6.
[186] Newshan G, Tsang P. Ritonavir and warfarin interaction. *AIDS* 1999;13:1788-9.
[187] Knoell KR, Young TM, Cousins ES. Potential interaction involving warfarin and ritonavir. *Ann Pharmacother* 1998;32:1299-302.
[188] Llibre JM, Romeu J, Lopez E, Sirera G. Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002;36:621-3.

* A comprehensive list of CYP inhibitors and inducers is available on the FDA website. Additional information is available via UpToDate, Clinical Pharmacology, and/or Facts and Comparisons

INR Testing Guidance:

- INR should be tested every 3 to 5 days until stable for all warfarin drug-drug interactions involving 2C9 inhibitors or inducers
- INR should be tested every 1 to 2 weeks until stable for all warfarin drug-drug interactions involving 3A4 or 1A2 inhibitors and inducers, or any 2C9, 3A4, or 1A3 substrates
- INR should also be tested at the end of treatment for medications taken for an acute period of time (e.g. antibiotics); empiric warfarin dose increases back to prior maintenance dose can typically be made at that time assuming the patient has experienced no other clinically relevant changes

Special Considerations: Amiodarone[189]

- Amiodarone and its active metabolite desethylamiodarone have strong inhibitory effects on CYP2C9, 3A4, and 1A2
- **Initiating therapy**: 10% to 25% warfarin reduction during the first week, followed by additional dose reductions up to 60%; may take over 4 weeks to reach maximum level of enzyme inhibition
- **Discontinuing therapy**: Given the long half-life of amiodarone (53 to 61 days), enzyme inhibitory effect will wear off over the course of 2 to 3 months. No empiric warfarin dose increase is required at the time of amiodarone discontinuation.

Additional Warfarin Drug Interaction Considerations	
Protein Binding	Warfarin is highly bound to plasma proteins (> 98%) and competition with other medications that are ≥ 90%[190] protein bound (e.g. doxycycline, clindamycin, ibuprofen, naproxen, furosemide, spironolactone) can cause warfarin displacement leading to increased INRs • Effect is typically seen 1 day to 3 weeks after drug initiation and effects are generally mild, transient, and do not require changes to warfarin therapy unless combined with a CYP450 inhibitor[27]
Acute Illness	Infection, diarrhea, vomiting, and acute decreases in appetite can impact INR stability and can have an additive effect with drug-drug interactions with antibiotics and other acute medications[191]
Intestinal Vitamin K Production	Administration of certain medications, including broad spectrum antibiotics (e.g. penicillin, amoxicillin, clindamycin, cephalexin), may negatively impact vitamin K-producing intestinal bacteria resulting in a reduction in vitamin K synthesis[192] • No empiric dose adjustments are generally required and INR should at least be tested at the end of the treatment course (more frequently if patient is acutely ill) • May have more of a significant effect in malnourished patients as the role of intrinsically produced vitamin K likely plays a larger role in clotting factor synthesis

[189] Kurnik D, Loebstein R, Farfel Z, et al. Complex drug–drug–disease interactions between amiodarone, warfarin and the thyroid gland. *Medicine (Baltimore)* 2004;83:107-13.
[190] Johnson-David KL, Dasgupta A. Special Issues in Therapeutic Drug Monitoring in Patients With Uremia, liver Disease, and in Critically Ill Patients. *Clinical Challenges in Therapeutic Drug Monitoring: Special Populations, Physiological Conditions and Pharmacogenomics.* 2016;11:245-260.
[191] Shikdar S, Vashisht R, Bhattacharya PT. International Normalized Ratio (INR). *StatPearls*. Treasure Island(FL): StatPearls Publishing;2021.
[192] Rice PJ, Perry RJ, Afzal Z, et al. Antibacterial prescribing and warfarin: a review. *British Dental Journal*. 2003;194:411-415.

Additive Effects	Interactions involving multiple mechanisms have an additive effect and may require higher empiric dose adjustments, for example: • High protein-binding CYP2C9 substrate • CYP1A2 inhibiting drug being used in an acutely ill patient • CYP3A4 inhibiting antibiotic that disrupts vitamin K production in GI tract

Appendix 13: Heparin-induced Thrombocytopenia (HIT)[193] [194] [195]

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening drug reaction to heparin (unfractionated or low molecular weight) resulting from autoantibodies directed against endogenous platelet factor 4 in complex with heparin. This antibody activates platelets and can cause, potentially resulting in catastrophic arterial and venous thrombosis. Complications include, but are not limited to, deep venous thrombosis, pulmonary embolism, ischemic limb necrosis, acute myocardial infarction, and stroke. HIT occurs infrequently in post-surgical patients, 2.6% of patients treated with unfractionated heparin and 0.2% of patients treated with LMWH. It most commonly occurs after orthopedic surgery.[196]

Patient population	Route of exposure	Incidence of HIT (%)
Postoperative patients	Heparin - prophylactic or therapeutic dose	1-5
	Heparin - flushes	0.1-1
	LMWH – prophylactic or therapeutic doses	0.1-1
	Cardiac surgery patients	1-3
Medical	Patients with cancer	1
	Heparin, prophylactic or therapeutic dose	0.1-1
	LMWH, prophylactic or therapeutic dose	0.6
	Intensive care patients	0.4
	Heparin, flushes	<0.1
	Obstetrics patients	<0.1

Clinical Manifestation/Context:

- New onset of thrombocytopenia (platelet count <150,000 beginning four or more days after starting any heparin; note that thrombocytopenia often precedes thrombosis.
- A drop of platelet count at least 50% even in the absence of thrombocytopenia, four or more days after starting any heparin.
- Venous or arterial thrombosis while on heparin or shortly after heparin is started.
- Necrotic skin lesions at heparin injection sites.
- Systemic symptoms, such as chills, cardiopulmonary arrest, dyspnea, fever, hypertension, or tachycardia, some days after heparin bolus.

[193] Linkins, Lori-Ann et al, Treatment and Prevention of Heparin-Induced Thrombocytopenia: Chest 2012;141;e495S-530S
[194] Coutre, Stephen. Clinical presentation and diagnosis of heparin-induced thrombocytopenia; UpToDate
[195] American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia; recommendation 3.7.b
[196] Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005; 106:2710.

Diagnosing HIT:

1. Use 4Ts Score to calculate risk of HIT (see table on next page, or use to http://www.mdcalc.com/4ts-score-heparin-induced-thrombocytopenia/ to calculate the risk of HIT). If score intermediate or high probability, make provisional diagnosis of HIT and order HIT antibody. If score low probability, presume patient does not have HIT. Specifics: if risk >1%, monitor platelet count every 2 to 3 days from days 4 to 14, or until heparin is stopped, whichever occurs first. Monitoring not required when risk is <1%.
2. Confirm diagnosis with testing for antibodies to platelet factor 4 (HIT antibodies), either positive ELISA with optical density (OD) >2.00 or positive functional assay for HIT antibodies. Note that presence of HIT antibodies is definitive, but often is not available for days. Additional clinical evaluation, including consultation with a consultant, may be required when conclusion is not entirely clear in this provisional review.
3. In patient with isolated HIT with no evident thrombosis, consider LENI to screen for asymptomatic venous thrombosis. In the presence of an upper extremity catheter, consider UENI.

Principles of management:

1. If HITT (HIT with thrombosis) or isolated HIT is present with normal renal function, stop heparin (or LMWH) and use a non-heparin anticoagulant, such as argatroban, bivalirudin, fondaparinux, or a direct oral anticoagulant (DOAC). Do NOT use heparin or warfarin.
2. If HITT (HIT with thrombosis) or isolated HIT is present with decreased renal function, stop heparin (or LMWH) and use argatroban at therapeutic doses or a DOAC (when permitted by extent of renal dysfunction), as argatroban is metabolized by the liver. Do NOT use heparin, LMWH, or warfarin.
3. If HITT (HIT with thrombosis) or isolated HIT is present with abnormal hepatic function and normal renal function, stop heparin (or LMWH) and use fondaparinux or DOAC, not warfarin.
4. The presence of a high bleeding risk may temper this decision. In the presence of a high bleeding risk with absence of evidence of thrombosis, use of these non-heparin anticoagulants may be deferred.
5. If HIT and severe thrombocytopenia, platelet transfusion indicated only in presence of active bleeding or procedure with high risk of bleeding.
6. Do not start warfarin until platelet count at least 150,000, and do not start with loading dose. DOACs preferred over warfarin in patients with clinically stable HIT with average risk of bleeding.
7. If patient is already on warfarin when HIT is diagnosed, administer vitamin K.
8. When warfarin is started or resumed, prescribe a 5-day overlap with non-heparin anticoagulant (as above); recheck INR after latter stopped.
9. If acute or subacute HIT present and patient requires percutaneous cardiac intervention, cardiac surgery, or renal dialysis, or is pregnant, see Kearon, C et al; Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb; 141(2 Suppl): e419S–e494S.
10. A patient with confirmed HIT antibodies should avoid heparin for life. When VTE treatment or prophylaxis is required, use a non-heparin anticoagulant (e.g., apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or warfarin).
11. If patient has past history of HIT, with new thrombosis unrelated to HIT and normal renal function, use a DOAC or fondaparinux in full therapeutic dose.
12. Note that the occurrence of thrombocytopenia, even in the context of heparin, still requires a definitive diagnosis when HIT has been ruled out. Consider other possibilities, such as disseminated intravascular coagulation/sepsis, immune thrombocytopenia, post-transfusion purpura, thrombotic microangiopathy, drug-induced thrombocytopenia, venous thrombosis unrelated to heparin, cardiopulmonary bypass, lupus or antiphospholipid antibody syndrome, and delayed-type hypersensitivity reactions to heparin.

4Ts Score[197]:

1. 4T'S score calculation:

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. **(Select only 1 option)**	○ > 50% platelet fall AND nadir of ≥ 20 AND no surgery within preceding 3 days	○ > 50% platelet fall BUT surgery within preceding 3 days OR ○ any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (eg, 30-50% platelet fall or nadir 10-19)	○ < 30% platelet fall ○ any platelet fall with nadir < 10
Timing (of platelet count fall or thrombosis*) Day 0 = first day of most recent heparin exposure **(Select only 1 option)**	○ platelet fall day 5-10 after start of heparin ○ platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	○ consistent with platelet fall days 5-10 but not clear (eg, missing counts) ○ platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days ○ platelet fall after day 10	○ platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) **(Select only 1 option)**	○ confirmed new thrombosis (venous or arterial) ○ skin necrosis at injection site ○ anaphylactoid reaction to IV heparin bolus ○ adrenal hemorrhage	○ recurrent venous thrombosis in a patient receiving therapeutic anticoagulants ○ suspected thrombosis (awaiting confirmation with imaging) ○ erythematous skin lesions at heparin injection sites	○ thrombosis suspected
oTher cause for Thrombocytopenia** **(Select only 1 option)**	○ no alternative explanation for platelet fall is evident	**Possible other cause is evident:** ○ sepsis without proven microbial source ○ thrombocytopenia associated with initiation of ventilator ○ other	**Probable other cause present:** ○ within 72 h of surgery ○ confirmed bacteremia/ fungemia ○ chemotherapy or radiation within past 20 days ○ DIC due to non-HIT cause ○ posttransfusion purpura (PTP) ○ platelet count < 20 AND given a drug implicated in causing D-ITP (see list) ○ non-necrotizing skin lesions at LMWH injection site (presumes DTH) ○ other

Drugs implicated in drug-induced immune thrombocytopenia (D-ITP)

Relatively Common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin
Less Common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: This is a partial list.

* Timing of clinical sequelae, such as thrombocytopenia, thrombosis, or skin lesions.
**Two points if necrotizing heparin-induced skin lesions even if thrombocytopenia not present.

2. 4T'S score interpretation:

- 0 to 3 points – Low probability of HIT
- 4 to 5 points – Intermediate probability of HIT
- 6 to 8 points – High probability of HIT

[197] Linkins, Lori-Ann et al, *Chest* 2012;141;e500S