Harvard Vanguard Medical Associates
Anticoagulation Management Service
CLINICAL GUIDELINE[1] AND PRACTICE PROTOCOL[2]

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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 Antithrombotic and Thrombolytic Therapy, 9th Edition: ACCP Guidelines; vol. 141 supplement CHEST-9). For access online, go to: http://journal.publications.chestnet.org/issue.aspx?journalid=99&issueid=23443&direction=P

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INTRODUCTION

The Anticoagulation Management Service (AMS) complements care provided by Harvard Vanguard Medical Associates primary care and specialty clinicians by educating patients, managing anticoagulation therapy, and monitoring response to therapy.

The AMS is available to all patients who receive their primary care through the Harvard Vanguard Medical Associates Internal Medicine practice. Patients enroll in AMS by receiving a referral from a primary care physician or collaborating prescribing clinician who is part of the HVMA practice.

AMS assumes full responsibility for day-to-day management of enrolled patients' oral anticoagulation therapy. The service operates 24/7, using an on-call system and coordinating with Telecom and the Weekend Urgent Care Program to provide after-hours care. Non-emergent interruptions in therapy, dose changes, or changes in INR monitoring schedules necessitated by institution of new medications, scheduled procedures, or other adjustments to the patient's treatment plan should ***always*** be done in coordination with the AMS.

ELIGIBILITY FOR ENROLLMENT

Only patients with HVMA PCPs may enroll in the AMS program. Either the PCP or other participating MD or APC may initiate the referral, which may be submitted by a delegate representing the responsible clinician.

REFERRAL AND ENROLLMENT

Steps in referral should include:

1. **Patient agreement:** Prior to referral, the referring clinician 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, HVMA secure email, or through an identified alternative contact.
2. **Initial testing:** Prior to initiating treatment, the referring clinician 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 contact the referring clinician to order the indicated test(s), 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).

3. **Prior warfarin dosing:** For any patient already on warfarin at the time of referral (for example, started during a hospitalization or care transferred from an outside physician to HVMA), the referring clinician is responsible for obtaining most recent INRs and doses to ensure safe transfer of care.
4. **Initial dosing:** The referring clinician 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.
5. **Basic education:** The referring clinician should provide basic education on the effects of warfarin, safety issues, reportable symptoms, and the importance of INR monitoring. Ideally, the patient should receive appropriate patient education materials at this time. These documents are available in the EpicCare Health Education Library, under Adult Medicine→Anticoagulation documents (ALL). Appropriate documents include Anticoagulation Fact Sheet, Warfarin and Medication Interactions, and Warfarin & Vitamin K. In situations when the referring clinician has not seen the patient before the referral (for example, when the patient has been started on anticoagulation during a hospitalization or ER visit), the AMS manager will insure that the patient receives these documents or similar documents available as SmartText within the EMR.
6. **Documentation:** The referring clinician 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.
7. **Target ranges:** The Anticoagulation Management Service operates under an approved guideline (this document), created in accordance with CHEST-9 guidelines and other evidence –based anticoagulation literature. 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 the AMS chief or physician consultant on receipt of referral, and must have a basis considered reasonable standard of care, not arbitrary or simply based on the personal preference of the referring clinician or consultant. In addition, the recommendation must be considered both possible and safe for the patient, as judged by the AMS chief or physician consultant. No case of this nature will be accepted in the Anticoagulation Management Service without this review. It is the responsibility of the AMS manager receiving the referral to consult the appropriate chief or physician consultant, and the responsibility of the chief or physician consultant to respond on the same business day. Examples of cases that might be considered reasonable though outside of guidelines include:
   - the indication of a higher goal or addition of antiplatelet agent in a patient previously treated at standard goal for atrial fibrillation, then having embolic TIAs 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:
   - the 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
   - the use of target ranges including any values below 1.8 for prevention of stroke in patients with atrial fibrillation
   - the 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 difference of 0.5 between the high and low end of target range will be accepted in any circumstances
8. **Feedback to referring physician:** The referring clinician and the patient's PCP will be notified via Epic message
   - if there is a 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.
   - when the patient is contacted and enrolled.

9. **Hospital discharges:** If the Anticoagulation Management Service learns of a discharged patient from case management, but has not received a referral, the AMS manager will immediately contact the PCP or other appropriate referring specialist (e.g. Cardiology or Orthopedics) to request a referral. The referring clinician is responsible for obtaining most recent INRs and doses to ensure safe transfer of care. Once complete information to facilitate transition of care has been received and contact made with the patient or designated caregiver, enrollment will 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, which are both considered indispensable to a safe transition of care.
10. **AMS management:** Once enrolled, the AMS will manage all subsequent INRs and dosing decisions 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.**

ASSESSMENT AND EDUCATION

Initial Assessment

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.

Patient Education

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

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- 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 compliance for dosing, testing, and appointments.* ***All patients (except those with goal of 1.5-2.0 for DVT/PE prophylaxis) 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 Anticoagulation 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, and 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.

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 Anticoagulation Management Service who are considering pregnancy should receive pre-conception counseling from the Obstetrics service.

Vitamin K in diet and supplements

All patients enrolled in the Anticoagulation Management Service 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 will provide 10-20mcg of vitamin K, which 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 addition al vitamin K supplement on a regular basis. However, patients already taking over-the-counter vitamin K 100 mcg with stable INR values may continue prior dosing. The availability of this supplement may be prudent for some 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 clinician) in managing the anticoagulation of referred patients in the HVMA practice. The PCP retains the medico-legal responsibility for care of these patients, since they are being managed by AMS managers by guideline protocol ordered by the PCP (or other participating clinician). When patients are intractably non-compliant, the PCP retains the responsibility for management of this non-compliance, too. The AMS will make every effort to contact patients overdue for INRs 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, following review of the case with the program chief or physician consultant.

The AMS secretary and manager outreaches to patients by phone calls, MyHealth e-mail messages, and/or letters after the patient's INR due date**.**

- **Patients who require frequent monitoring** (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 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 calls 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.
- **Patients who are actively being titrated to goal, but who do not fall into the above categories, and stable patients** are contacted according to the following schedule:
  1. At approximately 4-9 days after the INR due date, the AMS secretary makes an outreach reminder call or sends a MyHealth message.
  2. At approximately 13-17 days after the INR due date, the AMS secretary sends a "10 plus days overdue" letter to the patient's home requesting a call to the AMS service if unable to have an INR test within two days..

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3. At approximately 20-28 days after the INR due date, the AMS secretary sends a regular and certified letter to inform the patient that he/she is overdue well beyond safe management standards and will be disenrolled from the program, with care returned to the PCP if appropriate follow-up has not occurred within 10 more days. Disenrollment will only be taken after collaboration with the PCP, who will receive a copy of the letter.
4. At approximately 27-32 days after the INR due date, the AMS secretary reminds the AMS Manager to follow up with PCP regarding next steps.
5. At approximately 30-40 days after the INR due date, after review with the designated physician consultant, the patient is disenrolled from the AMS program and care is returned to the PCP. The AMS manager sends a disenrollment letter to the patient, cc'd to the PCP.

During 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 appropriate, the AMS manager may require 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 over the next 30-60 days, the patient may be disenrolled from the Anticoagulation Management Service as described above. In these cases, the PCP may need to adjust the patient's treatment plan to address non-adherence. Once care is returned, the PCP is responsible for discussing any treatment plan changes with the patient. Upon disenrollment, INR 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 compliance for a minimum of three months, the PCP can request re-enrollment by sending a new referral to the AMS. In some circumstances, when appropriate, re-enrollment may occur at an earlier date.

Patients who are managed outside AMS for 6 weeks or more (for example, patients with prolonged hospital or nursing home/rehab facility stays, care by other physicians during winter residence in Florida) will be temporarily disenrolled from the AMS program. The PCP or other referring clinician can request re-enrollment when the patient is ready to return to AMS management. When necessary, AMS managers will assist referring clinicians in completing referrals. However, the referring clinician remains responsible for providing updated information on recent INR results and warfarin doses and any changes in indication or INR goals.

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APPENDIX

Appendix I: GUIDELINE FOR ESTABLISHING INR GOAL AND DURATION OF TREATMENT

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, fondaparinux, warfarin, and rivaroxaban; see details in Appendix 8.
• 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	2.0-3.0	2.5	*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. Risk lower for provocation by surgery (1y: 1%; 5y: 3%) than other factors (estrogen therapy, pregnancy, injury or prolonged travel (1y: 5%, 5y: 15%) Risk higher for unprovoked (1y: 10%; 5y: 30%). If cancer present, risk estimated at 15%/year. If confined to distal veins, risk about half. If recurrent DVT, risk about 50% higher. Other factors include:* negative D-dimer testing 1 month after withdrawal of VKA (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). *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.*[4]
• 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).
• Patients with intermediate clinical suspicion of DVT/ PE awaiting diagnostic testing	N/A	N/A	Begin treatment immediately with agent for initial therapy if results are expected to be delayed >4 hours (see below).

[4] Duration of Long-term Anticoagulant Therapy, from Chest-2012-Kearon-Antithrombotic Therapy for VTE Disease - e419S-94S; 3.1

• 1st episode of DVT/PE due to transient, reversible identifiable risk factor	2.0-3.0	2.5	• All patients should receive initial treatment with 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. • 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	• All patients should receive initial treatment with 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. • 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	• LMWH or fondaparinux considered more effective than and preferred over warfarin. Warfarin preferred over dabigatran or rivaroxaban. Extended anticoagulation recommended for low/moderate bleeding risk and suggested for high bleeding risk. • 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	3 months (minimum duration) followed by risk benefit evaluation for long-term therapy. Considerations: • If first VTE is distal with no PE, 3 months usually sufficient for all bleeding risks. • 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. • 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) can be considered if increased bleeding risk or patient preference for less

			frequent monitoring, after at least 3 months at standard intensity)[5] [6] 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, warfarin preferred over dabigatran or rivaroxaban.
• 1st episode, high risk of recurrent thrombosis due to identifiable risk factor likely to persist	2.0-3.0	2.5	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.[7] When treatment is long-term, warfarin preferred over dabigatran or rivaroxaban.
• 2nd episode, whether or not cause identifiable, if cause unknown or not resolved	2.0-3.0	2.5	Lifetime (standard intensity 2.0-3.0 recommended for low bleeding risk and suggested for moderate bleeding risk; 3 months suggested for high bleeding risk. Note that low intensity 1.5-2.0 goal is not recommended in CHEST-9; 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, warfarin preferred over dabigatran or rivaroxaban.
• 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.

[5] 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

[6] "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

[7] 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. http://www.annals.org/cgi/content/full/146/3/204

• Superficial vein thrombosis (SVT) of lower limb of at least 5cm length	N/A	N/A	Prophylactic fondaparinux or LMWH for 45 days preferred over no treatment. Fondaparinux suggested over LMWH.
• Upper extremity DVT (involving axillary or more proximal veins)	2.0-3.0	2.5	Considerations: • Treatment protocol same as lower extremity DVT, using initial LMWH, IV UFH, or fondaparinux with 24-hour overlap at therapeutic INR with warfarin, continued for no less than 3 months • 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	Lifetime; 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
• **DV/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; 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.
Thrombophilias and DVT[8]			
a. **1st or subsequent episode <u>in the presence of high risk thrombophilia</u>**, 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 all other causes of thrombophilia d. One spontaneous life threatening event, such as massive near fatal PE, cerebral, mesenteric or portal vein thrombosis	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)

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

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			
• **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)			
• ->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)	Triple 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	-- 2.0-3i0 if warfarin used	-- 2.5 If warfarin used	CHEST9 suggests against antiplatelet agents and anticoagulation; if patient places high value on stroke prevention over potential bleeding complications, then warfarin reasonable[9]
• ->with identified acute LV thrombus (e.g. Takotsubo cardiomyopathy)	2.0-3.0 (3+ months)	2.5 (3+ months)	Anticoagulation at least 3 months suggested.
Atrial fibrillation with stable CAD	2.0-3.0	2.5	If patient chooses anticoagulation, warfarin suggested over combination warfarin and antiplatelet agents.
Atrial Fibrillation (AF) without valvular disease (includes paroxysmal and chronic AF and Atrial Flutter)[10]			CHEST-9 suggests dabigatran over warfarin for all nonvalvular AF and Atrial Flutter indications.
• **Low risk for ischemic stroke, TIA or systemic embolism: lone AF/flutter** (no risk factors, age<75, and no clinical or echocardiographic evidence of cardiomyopathy or valvular disease); CHADS2 = 0	N/A	N/A	CHEST-9 suggests against treatment with aspirin or anticoagulation. If treated, aspirin 75-325 mg suggested over anticoagulation or combination antiplatelet therapy. Treat with warfarin or dabigatran if strong patient preference after risk-benefit discussion).[11] The presence of several non-CHADS2 risk factors (female gender, age 65-74), presence of vascular disease) may favor warfarin.
• **Intermediate risk for ischemic stroke, TIA or systemic embolism: AF/flutter with one moderate risk factor,** either diabetes, hypertension, moderate to poor systolic function), or age 75+; CHADS2 = 1	2.0-3.0 if warfarin	2.5 if warfarin	CHEST 9 suggests anticoagulation over aspirin 75-325 mg daily or dual antiplatelet therapy; treatment recommended over no treatment; if anticoagulation declined, dual antiplatelet therapy suggested over aspirin alone, unless bleeding concern is reason for not using anticoagulation.
• **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), and age 75+; CHADS2 of 2 or more	2.0-3.0	2.5	Lifetime
AF/flutter managed with rhythm control			CHEST-9 suggests that management should follow same principles as above, regardless of persistence of normal sinus rhythm. After a successful ablation of atrial flutter, however, discontinuation of anticoagulation may be considered.

[9] 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.

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

[11] 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.

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Atrial F\fibrillation (AF) with valvular disease or prosthetic heart valve			
• **AF/flutter with rheumatic mitral valve disease**	2.0-3.0	2.5	Lifetime
• **AF/flutter with bioprosthetic mitral and/or aortic heart valve**	2.0-3.0	2.5	Lifetime; consider 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.
• **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.
• **AF/flutter with mechanical low-risk aortic heart valve**	2.5-3.5	3.0	Lifetime
• **AF/flutter with mechanical high-risk aortic heart valve or any mechanical mitral valve**	2.5-3.5	3.0	Lifetime; recommend addition of aspirin 81 mg unless patient at high risk of bleeding, such as in patients with history of GI bleed or >80 years of age.
Atrial Fibrillation/flutter, duration of at least 48 hours or unknown, with planned electrical or pharmacologic cardioversion			
• **Option 1**	2.0-3.0	2.5	• LMWH, dabigatran, 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.[12] • 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.
• **Option 2**	2.0-3.0	2.5	• IV UFH with target PTT of 60 (range 50-70s), LMWH in therapeutic doses, dabigatran 150mg bid or rivaroxiban 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).

[12] Assuming INR at least 2.0 for 3 weeks:
- 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.

			• 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, <u>duration <48 hours</u>, 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) • Anticoagulation 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. • Continue anticoagulation with warfarin at least 4 weeks after cardioversion regardless of risk factors.
Bioprosthetic (tissue) heart valves			
• **Aortic bioprosthetic (tissue) heart valves, first three months after replacement, no AF**	N/A	N/A	If no other indications for warfarin, aspirin 81 mg daily suggested for 3 months.
• **Aortic transcatheter bioprosthetic (tissue) heart valves, first three months after replacement, no AF** •			If no other indications for warfarin, aspirin 81 mg plus clopidogrel 75 mg daily suggested for 3 months.
• **Mitral bioprosthetic (tissue) heart valves, first three months after replacement, no AF**	2.0-3.0	2.5	• Warfarin suggested over aspirin for 3 months.
• **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; <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.

• **All bioprosthetic (tissue) heart valve plus LV dysfunction, pacemaker, large LA, embolic stroke, or hypercoagulable state**	2.0-3.0	2.5	Lifetime
Mechanical heart valves – all require bridging with LMWH or UFH until INR stable in therapeutic range. If UFH, prophylactic dose; if LMWH, may be prophylactic or treatment dose.			
• **Aortic mechanical valves + no other risk factors** o Low risk (low thrombogenicity) valves *plus* normal sized atrium: bileaflet valves (St. Jude, Carbomedics) and tilting disc valves (Medtronic Hall tilting disc) o Higher risk (higher thrombogenicity) valves: other tilting disk valves (Bjork-Shiley, Monostrut, Omnicience/Omnicarbon, Ultracor) and caged ball valves (Starr-Edwards)	2.0-3.0 2.5-3.5	2.5 3.0	Lifetime 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. Recommendations on these older valves based on prior review in CHEST-8; not revised in CHEST-9.
• **All mechanical valves + risk factors, including** AF, LV dysfunction, anterior-apical ST-segment elevation MI, LAE, low EF, or hypercoagulable state	2.5-3.5	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.
• **All mechanical valves + history of systemic embolus despite a therapeutic INR**	2.5-3.5	3.0	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.
• **Aortic mechanical valve with usual target of 2.5 plus any mitral mechanical valve**	2.5-3.5	3.0	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.
• **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 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
• **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 anticoagulation contraindicated; then anti-platelet agent
• **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	2.5	Lifetime
Anticoagulation during pregnancy			
• **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	LMWH at usually adjusted dose or 75% usual therapeutic dose, with resumption of warfarin post-partum.

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• **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			
• **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, rivaroxaban and dabigatran.
Effects of anticoagulation on nursing			
• **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.[13]
• **Enoxaparin (Lovenox and generics)**			Due to large molecular weight of 2000 to 8000 daltons, enoxaparin would not be expected to be

[13] See Lactmed: Warfarin

			excreted into breast milk. No special precautions are required.[14]
Pulmonary hypertension[15]			
• **Idiopathic pulmonary hypertension (confirmed by right heart catheterization)**	1.5-2.5	2.0	Anticoagulation part of core treatment due to increase in survival; duration = lifetime
• **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.

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. These valves require bridging with LMWH for all hold situations and when INR is below 1.8.
  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.
- 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

[14] See Lactmed: Enoxaparin
[15] 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

Duration of Anticoagulation after Unprovoked 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).

- Patients with VTE provoked by surgery generally benefit from 3 months of anticoagulation rather than 6 months or extended therapy. When VTE is provoked by a transient risk factor other than surgery, 3 months is recommended if there is high bleeding risk, and suggested if there is low or moderate bleeding risk.
- Patients with first unprovoked VTE with low to moderate bleeding risk benefit from extended anticoagulant therapy at standard intensity beyond initial 3 months of treatment **when significant thrombophilia is also present.** Patients at high bleeding risks 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.
- Patients with first unprovoked PE or proximal DVT should have consideration of extended therapy after 3 months of treatment. Extended therapy is suggested over 3 months of treatment when bleeding risk is low to moderate; three months of anticoagulation is recommended over extended therapy when bleeding risk is high. In the absence of significant thrombophilia, the risk of bleeding with extended therapy outweighs the risk of recurrent VTE or PE in patients with high bleeding risks.
- Patients with second unprovoked VTE should have consideration of extended therapy after 3 months of treatment. Extended therapy is recommended when bleeding risk is low and suggested when bleeding risk is moderate. Three months of treatment at standard intensity is suggested over extended therapy for patients at high bleeding risk.

Recommendations and Suggestions for Extended Anticoagulation after DVT/PE[16]			
	Low Bleeding Risk	**Moderate Bleeding Risk**	**High Bleeding Risk**
1st pulmonary embolism or proximal DVT post-surgery	**No more than 3 months therapy recommended**	**No more than 3 months therapy recommended**	**No more than 3 months therapy recommended**
1st pulmonary embolism or proximal DVT provoked by transient non-surgical risk factor	**3 months therapy suggested**	**3 months therapy suggested**	**No more than 3 months therapy recommended**
1st unprovoked pulmonary embolism or proximal DVT	**Extended therapy suggested**	**Extended therapy suggested**	**No more than 3 months therapy recommended**
1st distal DVT	**3 months therapy suggested**	**3 months therapy recommended**	**No more than 3 months therapy recommended**
Recurrent VTE	**Extended therapy recommended**	**Extended therapy suggested**	**3 months therapy suggested**
DVT in the presence of active cancer	**Extended therapy recommended***	**Extended therapy recommended***	**Extended therapy suggested***
Significant thrombophilia	**Extended therapy recommended**	**Extended therapy recommended**	**Extended therapy suggested****

** LMWH suggested over VKA; if VKA used, warfarin suggested over dabigatran/rivaroxaban. **Decision depends on relative risks of bleeding and clotting; must be individualized for patient.*

[16] Chest-2012-Kearon-Antithrombotic Therapy for VTE Disease - e432S

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	Low Risk (0 Risk Factors)	Moderate Risk (1 Risk Factor)	High Risk (≥2 Risk Factors)
Determination of bleeding risk for extended anticoagulation[17]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6	3.2	12.8
Anticoagulation after first 3 months			
Baseline risk (%/year)	0.3	0.6	2.5
Increased risk (%/y)	0.5	1.0	4.0
Total risk (%/y)	0.8	1.6	6.5

Bleeding Risk Factors (listed alphabetically without reference to extent of contribution of risk factors)

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

[17] Chest-2012-Kearon-Antithrombotic Therapy for VTE Disease - e432S. Consult original documentation for further details and explanation of risks.

Appendix 2: GUIDELINE FOR 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. 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.

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.
   - 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[18]:**

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
		3.1 – 3.5	0, 5, 5
		> 3.5	0, 0, 2.5
1.3 – 1.4	10, 10	< 2.0	15, 15, 15
		2.0 – 3.0	7.5, 5, 7.5
		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
		3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
1.7 – 1.9	5, 5	< 2.0	7.5, 7.5, 7.5
		2.0 – 3.0	5, 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
		3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
2.3 – 3.0	0, 2.5	< 2.0	5, 5, 5
		2.0 – 3.0	2.5, 5, 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

[18] 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, 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 of physician 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 of physician consultant.

INR Monitoring During Titration To Goal

1. INRs are monitored daily or every other day until the INR ≥ 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.

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).

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Appendix 3: GUIDELINES FOR MAINTENANCE DOSE ADJUSTMENT AND MONITORING

1- General Principles of 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.

2- Assessment Prior to Dose Change

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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 pills and the exact mg on the bottle(s) 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)? Look in medication history.
   - Inducers will lower INR levels (speed up the metabolism of warfarin). **Did patient START an inducer, such as phenytoin, phenobarbital, rifampin, or carbamazepine?**
   - Inhibitors will raise INR levels (slow down the metabolism of warfarin). **Did patient STOP an inhibitor, such as amiodarone, ciprofloxacin, 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 pills and the exact mg on the bottle(s) he/she is taking. 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, c] ↓	**INR 4.5-5.0**[b, c] ↓
Increase weekly dose by 10%-20% ↓	Decrease weekly dose by 10% to 20% ↓	Hold dose for 1-2 days, then consider rechecking INR before decreasing weekly dose by 15%-20% ↓	Hold two doses, then recheck INR before decreasing weekly dose by 20% ↓
Monitor INR within 2 weeks	Monitor INR within 2 weeks	Monitor INR within 1week of changed dose	Monitor INR within one week of changed dose

[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] If the INR is ≥3.8 but less than 5.0, with or without an identifiable cause for the high INR, hold dose for 1-2 days and consider rechecking INR before reducing dose. If lab error suspected (uncommon but possible), recheck INR same day or at latest one day after held dose.

[c] INR values 4.0 and above done by fingerstick at HVMA 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[d] ↓	**INR 4.1-4.5[e, f]** ↓	**INR 4.6-5.0[e, f]** ↓
Increase weekly dose by 10%-20% ↓	Decrease weekly dose by 10%-20% ↓	Hold dose for one day and consider rechecking INR before decreasing weekly dose by 15%-20% ↓	Hold two doses and recheck INR before decreasing weekly dose by 20% ↓
Monitor INR within 2 weeks	Monitor INR within 2 weeks	Monitor INR within one week of changed dose	Monitor INR within one week of changed dose

[d] 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.

[e] If the INR is ≥4.1 but less than 5.0, whether or not there is an identifiable cause for the high INR, hold dose for 1-2 days and consider rechecking INR before reducing dose. If lab error is suspected, recheck INR same day or at latest after one held dose.

[f] INR values 4.0 and above done by fingerstick at HVMA 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[19, g]

INR <1.3	**INR ≥1.3 and <1.5**	**INR >2.0 and ≤3.0**	**INR >3.0 and ≤4.0**	**INR >4.0**

[19] 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

Increase current dose by 15%- 20% ↓	Increase current dose by 10%-15% ↓	Decrease current dose by 10%-15% ↓	Decrease current dose by 15%-20% ↓	Stop drug for 3 days and repeat INR. If INR remains >4.0, discontinue therapy.
Monitor INR within one week	Monitor INR within 2 weeks	Monitor INR within 2 weeks	Monitor INR within one week	Monitor INR on day 4.

[g] Apply above monitoring considerations; however, note that main advantage of using this range for long-term prevention of DVT/PE relates to anticipated 8-week testing intervals.

Therapeutic INR Range of 1.8-2.3 [h]

INR <1.5	**INR 1.6-1.7**	**INR 1.8-2.3**	**INR 2.4-3.0**	**INR 3.1-3.5**	**INR >3.6**
Increase current dose by 15% ↓	Increase current dose by 10% ↓	Continue current dose ↓	Decrease current dose by 10% ↓	Decrease current dose by 15% ↓	Hold dose for 1 days, then recheck INR before decreasing dose by 15%-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.

6- INR Monitoring Standards for Patients on Maintenance Therapy

1. Most patients with indications other than "history of DVT/PE with no identifiable cause; target range 1.5-2.0" should have INR checked at least monthly.
2. Patients with indication "history of DVT/PE with no identifiable cause" and an INR range of 1.5-2.0 may have INR checked every 8-12 weeks, as long as results remain stable and in therapeutic range.
3. 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. 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.
4. 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

1. Prescriptions for new drugs likely to interact with warfarin will generate an alert to the AMS manager.
2. Patients are also expected to report to AMS manager whenever starting or stopping a drug with known interaction with warfarin.
3. An INR will be checked 3-5 days after a patient starts or stops any drug likely to interact with warfarin, and subsequently as indicated.
4. Amiodarone and certain other drugs warrant dose reduction prior to 3-day check.[20]
5. INR must be monitored repeatedly during Amiodarone starts and tapers, since this drug may have delayed effects.

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. Repeat INR within one week. Bridging is only required if otherwise indicated by CHADS2 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):

[20] Warfarin dose should be reduced approximately 50% when the patient is started on Amiodarone. Also, consider immediate warfarin dose reductions when patient is started on Flagyl (metronidazole), Bactrim (sulfamethoxazole/trimethoprim), or Diflucan (fluconazole).

- CV will be performed at INR 2.0-4.2.
  - Cardiologist will make case-by-case decision for INR in range 4.2-5.0.
  - CV will be postponed at INR >5.0 – AMS manager will notify cardiologist to coordinate plan.

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):

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 CHADS2 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 four 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 four 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 four 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[21]

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.

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

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.
2. Monitoring during this time will follow usual testing guidelines, with bridging based on the CHADS2 or other relevant risk factors when and if required.

11- INR Monitoring Standards for Pacemaker and AICD Placement/Revision and Radiofrequency Ablations

1. These procedures require communication between the AMS manager and electrophysiologist prior to development of a plan for holding warfarin. Some procedures can be done on therapeutic warfarin dose, which reduces risk for situations where risk of thrombosis is high, such as mechanical mitral valves, particularly in the presence of atrial fibrillation. If indication for anticoagulation is simply low to moderate risk atrial fibrillation, a hold of warfarin would likely be appropriate.
2. Depending on the situation, one of the following scenarios may occur:
   - Warfarin hold: warfarin may be held 5 days from baseline ~2.5, or 7 days from baseline ~3.0 or above to achieve an INR below 1.6 on the day preceding the procedure.
   - Bridge: If high risk indication requires bridging (see Appendix 7), LMWH will begin 2 days after start of initial hold, and continue until the day before the procedure, 24+ hours before the procedure, with last dose 50% of the total daily dose.
   - If high-risk indication and electrophysiologist is willing to proceed with therapeutic INR, AMS manager will simply insure that INR is 2.0-3.4 within the week prior to the procedure, which may proceed without holding warfarin or requiring a bridge with LMWH.
3. Post-procedure resumption of warfarin or use of post-procedure LMWH also follows the usual perioperative management protocol, which requires the surgeon or cardiologist to clear the patient to resume anticoagulation.
   - **Resume pre-procedure warfarin dosing**: Except in unusual circumstances where hemostasis has not been maintained, patients may resume warfarin at usual dose the evening of the procedure.
   - **LMWH per electrophysiologist only:** Due to the risk of creating a pocket hematoma with use of LMWH following these procedures, resumption of LMWH (if indicated) always requires the specific instructions and clearance of the electrophysiologist, and cannot be determined or recommended prior to the procedure. If indicated, the electrophysiologist will communicate to the AMS manager and patient the date of resumption and dose of LMWH. Options include (1) no LMWH, (2) prophylactic dose enoxaparin 30 mg bid or 40 mg qd, (3) full dose enoxaparin 1 mg/kg bid or 1.5 mg/kg qd, or (4) transition from prophylactic dose to full dose.
   - **Discontinuation of LMWH:** The AMS manager will discontinue LMWH, if prescribed, once INR reaches therapeutic range.

Appendix 4: GUIDELINE FOR INITIAL OUTPATIENT TREATMENT OF VENOUS THROMBOSIS AND PULMONARY EMBOLUS[22]

Target Population:

Inclusion:

- Hemodynamically stable patients with newly confirmed VTE and newly confirmed or suspected pulmonary embolus

Relative exclusion:

- Pregnant patients
- Patients with decreased renal function (defined as CrCl of <30 ml/min)
- Patients who may require monitoring using an anti-factor Xa activity: morbidly obese (>150 kg)

Exclusion:

- Patients with arterial thromboembolism, dialysis, active bleeding or high risk for active bleeding, or with other severe uncompensated co-morbid conditions.

Treatment

Day One

- **Baseline laboratory evaluation:**
  a. Prothrombin time (PT) and calculated International Normalized Ratio (INR)
  b. Activated Partial Thromboplastin Time (aPTT) if patient has known coagulopathy, suspected lupus inhibitor, or liver disease.
  c. Serum creatinine – if not known
  d. Complete Blood Count (CBC), primarily to have baseline platelet count, but also to have baseline hemoglobin in event of bleeding
  e. HCG, if indicated
- **LMWH/Fondaparinux options:**
  a. Enoxaparin sodium (Lovenox) 1 mg/kg subcutaneously (sc) every 12 hours or 1.5 mg/kg (sc) once daily[23]
  b. Fondaparinux
    - If patient weighs <50 kg, Fondaparinux 5 mg subcutaneously once daily
    - If patient weighs 50-100 kg, Fondaparinux 7.5 mg subcutaneously once daily
    - If patient weighs >100 kg, Fondaparinux 10 mg subcutaneously once daily
- **Warfarin prescriptions:** 2.5 mg tablets per protocol (see Appendix 2)
  - If <75 years old, advise 5 mg (two 2.5 mg tablets) each night for 3[24] nights, then check morning INR. For healthy patients with no comorbidities, consider starting at 10 mg (four 2.5 mg tablets) for two days and then check morning INR as noted in Appendix 2 above.

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

[23] Per Kearon-Antithrombotic Therapy for VTE Disease - CHEST-2012; e419S-94S; 5.4.2: "*In patients with acute PE treated with LMWH, we suggest once- over twice-daily administration (Grade 2C). Remarks: This recommendation 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 once-daily dosing is impractical or impossible..*

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- If 75+ years old, advise 2.5 mg (1 tablet) each night for 2[25] nights, then check morning INR

- **Referral to anticoagulation management service:**
  1. Follow protocol posted in Epic "Health Education" in Anticoagulation documents.
  2. PCP or PCP surrogate, including any HVMA clinician involved in decision to anticoagulate the patient, can make referral.
  3. Enter referral by typing "anticoag…" in orders
  4. **Referral must include indication, INR target range, 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 3PM on Friday; otherwise, anticoagulation management of the patient remains the responsibility of PCP or PCP surrogate until the next business day.**
  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 PCP or PCP surrogate at all times.
  8. The PCP or PCP surrogate must write prescriptions for warfarin and LMWH/Fondaparinux.
  9. In situations requiring consideration of bridge therapy, the AMS manager will make recommendation to PCP or PCP delegate based on guideline and/or consultation with the chief or physician consultant. PCP or PCP delegate 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 recommendation to PCP or PCP delegate based on guideline and/or consultation with the AMS chief or physician consultant. Depending on the clinical situation, the AMS chief or physician consultant, PCP, or PCP delegate will make the final decision regarding the need for administration of Vitamin K. After hours and on weekends, the AMS chief or physician consultant or available AMS manager will typically make this decision and work with Telecom, Urgent Care, or the evening or weekend AMS manager to order the Vitamin K. 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: Guidelines 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 INRs in therapeutic range

Recommend use of compression stockings within one month of diagnosis of proximal DVT, to be continued a minimum of one year after diagnosis, to help prevent postphlebitic syndrome.[26]

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[24] 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).

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

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 should delay hospital transport. PCC and FFP work immediately; even IV vitamin K, though having more rapid onset of action than oral vitamin K, takes hours.
3. If patient is not bleeding and there is very good reason to doubt results (e.g. short draw of venous INR), consider rechecking 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.
4. CHEST-9 suggests against use of vitamin K to reverse INR elevations in the 5.0 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 patient-important outcomes, such as decrease in major bleeding. 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.[27i] Therefore, acknowledging the paucity of supporting (and contrary) evidence, we recommend that patients with an elevated INR 5.0-10.0 ***without significant bleeding*** undergo a four-step process, including:
    1. 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?
    2. Determination of bleeding risk score.
    3. 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 increasing the effect of warfarin or decreasing its metabolism.
    4. Development of plan for patient management, including at minimum holding warfarin and antiplatelet agents until INR in range or approaching therapeutic range, a multivitamin (or preferably, if available, vitamin K 200 mcg - available OTC as 100 mcg tabs), and close follow-up of the INR.

    In general, the consideration driving this decision for patients with INR 4.0-10.0 without significant bleeding depends on the condition(s) most likely to result in bleeding, such as a high bleeding risk score, a recent condition likely to predispose to bleeding (e.g. recent bleeding or invasive procedure), concurent use of an antiplatelet agent, and/or prolongation of the high-INR state despite holding warfarin. When any of these conditions exists, vitamin K should be considered. When all are absent, it is usually safe to simply hold warfarin and closely follow the INR.

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[26] 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.

[27] 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:

Bleeding Risk Assessment Tool[28]	
Bleeding Risk Factors	**Bleeding Risk Factor Points**
Age ≥ 65 years	1
History of Stroke	1
History of Gastrointestinal Bleed within last two weeks	1
One or more of the following (equals one): Recent myocardial infarction Hematocrit <30 percent Serum creatinine concentration >1.5 mg/dl Diabetes mellitus	1
Bleeding Risk Score	**Bleeding Risk Category**
0	Low
1-2	Moderate
3+	High

CHEST-2012 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:[29]

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

[28] Adapted from Beyth, RJ, Quinn, LM, Landefeld, CS. *Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin.* Am J Med 1998; 105:91.

[29] Adapted from Chest-2012-Kearon-Antithrombotic Therapy for VTE Disease - e432S. Consult original document for further details and explanation of risks.

Application of Bleeding and Bleeding Risk Assessment to Clinical Scenarios[30]:

Clinical Scenario I: Patient is bleeding:

INR	Bleeding Risk Category	Guideline Plan:
Minor bleeding with INR ≥ 5.0	*All: critical actions*	• **Notify AMS MD of INR and clinical description of bleeding.** • **AMS MD advises clinical action if evaluation or other action required[31].** • **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 AMS MD.**

Clinical Scenario 2: Patient is not bleeding, but has INR 5.0 to10.0 (note that the following recommendations do not conform to the suggestions provided in CHEST-9, but extend the considerations to clinical scenarios that involve increased risk of bleeding, not included in CHEST-9):

Clinical context	Bleeding Risk Score	Factors likely to interfere with INR returning to therapeutic range	Guideline Plan:
Patient taking aspirin and/or other antiplatelet drug, and/or has had recent procedure that would increase likelihood of bleeding	All	Present	• **Immediately advise patient to take vitamin K 2.5 mg and omit dose of warfarin. Vitamin K may be ordered by AMS manager in name of AMS MD.** • **Report intervention to AMS MD and PCP; consultation not required. However, if there is concern about INR falling to levels below therapeutic range due to past experience with patient in similar circumstances, INR elevated but in relatively low range (5.0-6.0), or very high thrombotic risk, consult AMS MD.** • **Closely monitor the INR. If the INR is not substantially reduced in 24-48h, continue close monitoring of INR, giving additional vitamin K as necessary.** • **Therapy is resumed at a lower dose per protocol when the INR is within or approaching therapeutic range.**

[30] Guideline plans are color-coded for easy reference, including:
- **Required consultation with AMS MD before taking clinical action noted in red.**
- **Notification of AMS MD after clinical action noted in green.**
- **Otherwise, action by AMS manager is by guidelines and does not require report to AMS MD or PCP.**

[31] 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.

Patient taking aspirin and/or other antiplatelet drug, and/or has had recent procedure that would increase likelihood of bleeding	Low or moderate risk	Absent	• **Report indication/target range, INR, bleeding risk, presence of anti-platelet agent, and absence of other relevant clinical circumstances to AMS MD.** • **The AMS MD may request administration of Vitamin K 1.25 to 2.5 mg po; if not advised, then tell patient to take a multivitamin, or preferably, if available, vitamin K 200 mcg (available OTC as 100 mcg tabs).** • **Omit the next dose of warfarin.** • **Repeat INR in 1-2 days; then reduce the weekly dose and resume treatment per protocol when INR is in or approaching therapeutic range.**
Patient taking aspirin and/or other antiplatelet drug, and/or has had recent procedure that would increase likelihood of bleeding	High risk	Absent	• **Immediately advise patient to take vitamin K 2.5 mg and omit dose of warfarin. Vitamin K may be ordered by AMS manager in name of AMS MD.** • **Report intervention to AMS MD and PCP; consultation not required. However, if there is concern about INR falling to levels below therapeutic range due to past experience with patient in similar circumstances, INR elevated but in relatively low range (5.0-6.0), or very high thrombotic risk, consult AMS MD.** • **Closely monitor the INR. If the INR is not substantially reduced in 24-48h, continue close monitoring of INR, giving additional vitamin K as necessary.** • **Therapy is resumed at a lower dose per protocol when the INR is within or approaching therapeutic range.**
Patient **not** taking aspirin or other antiplatelet drug, with **no** recent procedure that would increase likelihood of bleeding	Low or moderate	INR <u>likely</u> to decrease with holding warfarin	• **Advise taking multivitamin, or preferably, if available, vitamin K 200 mcg (available OTC as 100 mcg tabs). If neither available, no treatment is required.** • **Omit next dose or two and monitor INR before making additional adjustments.** • **Resume therapy at lower dose when INR is in therapeutic range** • **Report to AMS MD not required.**
Patient **not** taking aspirin or other antiplatelet drug, with **no** recent procedure that would increase likelihood of bleeding	Low or moderate	INR <u>not likely</u> to decrease with holding warfarin	• **Report indication/target range, INR, bleeding risk, absence of anti-platelet agent, and presence of factors that may cause INR to remain high AMS MD.** • **The AMS MD may request administration of Vitamin K 1.25 to 2.5 mg po.; if not advised, then tell patient to take a multivitamin, or preferably, if available, vitamin K 200 mcg (available OTC as 100 mcg tabs).** • **Omit the next dose of warfarin.** • **Repeat INR next day; then reduce the weekly dose and resume treatment per protocol when INR is in or approaching therapeutic range.**
Patient **not** taking aspirin or other antiplatelet drug, with **no** recent procedure that would increase likelihood of bleeding	High	Present or absent	• **Immediately advise patient to take vitamin K 2.5 mg and omit dose of warfarin. Vitamin K may be ordered by AMS manager in name of AMS MD.** • **Report intervention to AMS MD and PCP; consultation not required. However, if there is concern about INR falling to levels below therapeutic range due to past experience with patient in similar circumstances, INR elevated but in relatively low range (5.0-6.0), or very high thrombotic risk,**

			consult AMS MD. • **Closely monitor the INR. If the INR is not substantially reduced in 24-48h, continue close monitoring of INR, giving additional vitamin K as necessary.** • **Therapy is resumed at a lower dose per protocol when the INR is within or approaching therapeutic range.**

Clinical Scenario 3: Patient is not bleeding, but has INR ≥10.0:

Clinical context	Bleeding Risk Score	Factors likely to interfere with INR returning to therapeutic range	Guideline Plan:
All	All	Present or absent	• **Immediately advise patient to take vitamin K 5 mg and omit dose of warfarin. In some circumstances, when INR is extremely high and/or patient is at high risk of bleeding, it is reasonable to recommend 10 mg vitamin K. Arranging vitamin K for the patient should not await consultation with AMS MD. Vitamin K may be ordered by AMS manager in name of AMS MD.** • **Report intervention to AMS MD, 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.** • **Closely monitor the INR. If the INR is not substantially reduced in 24-48h, continue close monitoring of INR, giving additional vitamin K as necessary.** • **Therapy is resumed at a lower dose per protocol when the INR is within therapeutic range.**

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.
        a. Inducers will lower INR levels (speed up the metabolism of warfarin). Did patient START an inducer, such as phenytoin, phenobarbital, rifampin, or carbamazepine?
        b. Inhibitors will raise INR levels (slow down the metabolism of warfarin). Did patient STOP an inhibitor, such as amiodarone, ciprofloxacin, cimetidine, fluconazole, clarithromycin, erythromycin, metronidazole, or sulfamethoxazole/trimethoprim?
    d) **Diet:** Has patient increased vitamin K in diet (i.e. more dark, green leafy vegetables)?
    e) 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 is 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 greater than 0.5 below target range→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 of the target range→ 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 very high risk of clotting (e.g. two mechanical prosthetic valves, atrial fibrillation with CHADS2 score of 5+) and/or is in early management stage of acute venous thrombosis (e.g. DVT/PE within 3 months); consult AMS clinician in these circumstances.
    - **<u>Stable regimen, new circumstances:</u>** 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.
        - If patient is not at goal at 1st recheck, assess as an "active management" patient.

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- **Active management" regimen:**
    - Adjust warfarin dosing and monitor INR response per Appendix 3.
    - If INR is more than 0.2 below goal, Anticoagulation manager will assess the patient's risk and recommend bridging with LMWH/Fondaparinux if appropriate. See ***Thromboembolic Risk Assessment.***

4. Consult AMS clinician as advised in *Thromboembolic Risk Assessment* or other situations when treatment decision is not straightforward; notify PCP when directed by AMS MD.
    - If there are special considerations, the Anticoagulation manager will present the case to the AMS MD for review.
    - The AMS MD makes a treatment recommendation, which generally will be enacted by the AMS manager.

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.
    - The PCP is responsible for arranging for self-injection teaching,when required, and making alternative arrangements, such as nursing visits or office visits, if needed. The AMS manager will assist in this process.
    - The Anticoagulation manager will 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 AMS MD, and the AMS MD 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 comments of Coumadin Questionnaire 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.

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

Enoxaparin (Lovenox®), LMWH:

Full Dose.

- First choice: LMWH 1 mg/kg SC BID.
- Second choice: LMWH 1.5 mg/kg SC QD.

Prophylactic Dose

- LMWH 30 mg SC bid or 40 mg SC qd. Dose is not weight-based.

Special considerations (for further details, consult DRUGDEX®):

- CrCl less than 30 mL/min: Inpatient treatment of DVT, with or without PE: 1 mg/kg subcutaneously once daily, continue for a minimum of 5 days and up to 17 days s
- CrCl less than 30 mL/min: Outpatient treatment of DVT without PE: 1 mg/kg subcutaneously, continue for a minimum of 5 days and up to 17 days
- CrCl less than 30 mL/min: For prophylactic dose, use 30 mg SC qd.
- 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.[32]

Fondaparinux (Arixtra®):

Full Dose

- If patient weighs <50 kg, Fondaparinux 5 mg SC qd.
- If patient weighs 50-100 kg, Fondaparinux 7.5 mg SC qd.
- If patient weighs >100 kg, Fondaparinux 10 mg SC qd.

Prophylactic Dose

- Fondaparinux 2.5 mg SC qd. Dose is not weight-based.

Special considerations (for further details, consult DRUGDEX®):

- CrCl 50-80 mL/min: 25% reduction in total clearance; consider empiric dosage reduction
- CrCl 30-50 mL/min: 40% reduction in total clearance; consider empiric dosage reduction
- CrCl <30 mL/min: contraindicated
- Age greater than 75 years: use with caution, consider empiric dosage reduction

Dalteparin (Fragmin®):

[32] Chest-2012-Holbrook-Evidence-Based Management of Anticoagulant Therapy -e152S-84S.

Condition	Dose
Abdominal surgery (DVT prophylaxis):	
• *Low to moderate DVT risk*	2500 IU 1-2 hours prior to surgery, then qd for 5-10 days postoperatively
• *High DVT risk*	5000 IU the evening prior to surgery and qd for 5-10 days postoperatively.
• *Malignancy*	2500 IU 1-2 hours prior to surgery and 12 hours later, then 5000 IU qd 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 qd; start at least 6 hours after postsurgical dose
• *Preoperative (starting day of surgery):*	Initial: 2500 IU within 2 hours before surgery. Adjustment: 2500 IU 4-8 hours***** after surgery. Maintenance: 5000 IU qd; start at least 6 hours after postsurgical dose
• *Preoperative (starting evening prior to surgery)*	Initial: 5000 IU 10-14 hours before surgery. Adjustment: 5000 IU 4-8 hours***** after surgery. Maintenance: 5000 IU qd, 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.
Venous thromboembolism (cancer patients):	Initial (month 1): 200 IU/kg up to18,000 IU qd for 30 days. Maintenance (months 2-6): ~150 IU/kg up to18,000 IU qd. 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. If EGFR <30, monitor anti-Xa levels to determine appropriate dose.
Immobility/acute illness (DVT prophylaxis):	5000 IU qd

*Table adapted from **DRUGDEX®***

Special considerations:

- CrCl <30 mL/min - manufacturer recommends monitoring factor Xa levels
- Hepatic insufficiency – use with caution

Venous Thromboembolic Risk Assessment:[33]

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 "bridge" for low INR, planned or unplanned (if unclear, consult AMS clinician; see note below[34])
LOW RISK of Venous Thromboembolic Event (consultation with AMS clinician not required)	• DVT/PE >12 months ago and no other risk factors	<4	Treat with warfarin when indicated (does not apply to heterozygous factor V Leiden mutation with no prior history of DVT)	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR <1.4; however, consider using prophylactic dose during post-operative period if prolonged bedrest expected or any casting involved.
	• 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 appropriate for the inherent risk of the situation)			
	• Patients with heterozygous factor V Leiden mutation and history of DVT/PE >12 months ago, no other predisposing issues (risk of recurrence is virtually the same as the risk of recurrent DVT/PE when no predisposing factor has been found)			
	• 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 of Venous Thromboembolic Event (consultation with AMS clinician generally required, unless previous consultation has been completed and no clinical changes have occurred)	• Brief subtherapeutic INR with history of DVT/PE in the setting of a therapeutic INR	not quantified	Treat with warfarin	• Bridging LMWH recommended in many circumstances, especially if very low INR (below 1.4), expected hold ≥1 week, or current circumstance likely to increase risk of clotting (such as bedrest, surgery, or prolonged plane or car ride). Unless patient in active treatment phase or has additional risk factors, bridging usually not done for isolated low INR within 0.5 of lower end of target range. • Note that surgery itself increases the risk of post-operative thrombotic events, probably related to stimulation of the coagulation cascade by surgery. Therefore, the indication for LMWH in the post-operative period would be greater than the indication for an incidentally noted low INR value,
	• Brief subtherapeutic INR with history of DVT/PE in the setting of a hypercoagulable state, except as noted below under high risk thrombophilia			
	• A history of recurrent DVT/PE, due to specific condition no longer present			
	• A 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.			
	• DVT/PE with active cancer (treated within 6 months or palliative stage)			

[33] 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.

[34] Recommendations (if decision not straight-forward, consult with AMS clinician regarding decision on use of LMWH -- generally pertains to patients at "moderate risk", patients not previously treated to guideline, or patients with possible contraindications to use of LMWH. Remember that thromboembolic event relates not just to the risk of the patient, but also to the duration of interruption, and in general is decreased by about 50-67% by use of LMWH. The CHADS2 tables below provide a view to the number of prevented strokes by using LMWH in these situations. If, for example, there are 2 strokes for every 1000 patients during a one-week interruption of adequate therapy, and LMWH prevents half the expected strokes, then 999 patients in this risk range would have to be treated with LMWH to prevent one stroke. The final component of risk determination includes an assessment of the additional bleeding risk when LMWH is used. The ultimate decision to use or not use LMWH depends on the comparison of these risks, and must be presented to and understood by the patient. Additional factors, such as the inconvenience and costs to the patient, should also be considered.

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	• DVT/PE 3 to 12 months, when extended treatment considered appropriate (applies to patients receiving extended therapy due to high-risk thrombophilia, active cancer, recurrent DVT/PE, and unprovoked DVT/PE)			or even for the pre-operative period. In some circumstances, patients may need post-operative but not pre-operative bridging. • For brief (<one week) subtherapeutic INR or expected hold, consider enoxaparin at prophylactic dose (30 mg SC bid or 40 mg SC qd). If not contraindicated by risk of bleeding, this management is recommended early in the post-operative period whenever bedrest is expected or any casting is involved. • For prolonged (≥1 week) subtherapeutic INR or expected hold, or in some circumstances when INR <1.4, consider enoxaparin 1 mg/kg bid or 1.5 mg/kg qd) while INR is subtherapeutic. Depending on clinical circumstances, prophylactic dosing may be appropriate.
HIGH RISK of Venous Thromboembolic Event (consultation with AMS clinician not required)	• DVT/PE within 3 months	not quantified	Treat with warfarin	Postpone procedures requiring warfarin cessation when possible. Use enoxaparin 1 mg/kg bid (or 1.5 mg/kg qd if twice daily dosing infeasible whenever INR is subtherapeutic. In event of unavoidable, planned procedure, begin bridging prior to procedure and resume after procedure when cleared by surgeon. If full dose LMWH prohibited by bleeding risk during post-operative period, strongly consider prophylactic dose LMWH once hemostasis is secured.
	• A prolonged subtherapeutic INR with history of DVT/PE in the setting of a therapeutic INR	20+		
	• A prolonged subtherapeutic INR with history of DVT/PE in the setting of a hypercoagulable state			
	• A history of recurrent DVT/PE, due to specific condition still present			
	• High risk thrombophilia, defined as one of the following: a. One spontaneous event plus antiphopholipid syndrome[35], deficiency of antithrombin, protein C, or protein S, or multiple abnormalities b. Two or more spontaneous events plus all 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 e. One spontaneous in regular location and in setting of more than one genetic factor for thrombophilia			
	• All causes of thrombophilia are considered high risk in high risk situations (e.g. surgery, travel, immobilization in cast, need for bedrest for any condition); note that patients with heterozygous factor V Leiden mutation have the same risk for a thrombotic event as the rest of the general population, and do not need prophylaxis beyond what would be appropriate for the inherent risk of the situation.	not quantified		

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

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Arterial Thromboembolic Risk Assessment:[36]

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 "bridge" for low INR, planned or unplanned (if unclear, consult AMS clinician; see note below[37])
LOW RISK of Arterial Thromboembolic Event (consultation with AMS clinician not required)	• Lone atrial fibrillation (no co-morbidities and age = <75; CHADS2 risk score = 0 (see below)	1.4	No treatment (suggested in CHEST-9) or treat with aspirin 81--325 mg daily (only use anticoagulant if strong patient preference after risk-benefit discussion)[38]	Strong patient preference or other non-CHADS2 risk factors such as female sex and age 65+ may favor treatment with antiplatelet agents. If on warfarin, LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)
	• Atrial fibrillation plus only one of the following risk factors: age**≥75**, history of hypertension, diabetes, moderately or severely impaired left ventricular systolic function and/or heart failure (and no history of stroke). CHADS2 risk score = 1 *(see CHADS2 table, below)*.	3.1	Anticoagulant suggested over aspirin 81-325 mg daily and dual antiplatelet agents (aspirin + clopidogrel); CHEST-9 suggests dabigatran over warfarin; both are reasonable options depending on cost and patient convenience issues; aspirin considered reasonable alternative depending on clinical circumstances and preferences of patient	If on warfarin, LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)

[36] 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.

[37] Recommendations (if decision not straight-forward, consult with AMS clinician regarding decision on use of LMWH -- generally pertains to patients at "moderate risk", patients not previously treated to guideline, or patients with possible contraindications to use of LMWH. Remember that thromboembolic event relates not just to the risk of the patient, but also to the duration of interruption, and in general is decreased by about 50-67% by use of LMWH. The CHADS2 tables below provide a view to the number of prevented strokes by using LMWH in these situations. If, for example, there are 2 strokes for every 1000 patients during a one-week interruption of adequate therapy, and LMWH prevents half the expected strokes, then 999 patients in this risk range would have to be treated with LMWH to prevent one stroke. The final component of risk determination includes an assessment of the additional bleeding risk when LMWH is used. The ultimate decision to use or not use LMWH depends on the comparison of these risks, and must be presented to and understood by the patient. Additional factors, such as the inconvenience and costs to the patient, should also be considered.

[38] 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.

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	• Atrial fibrillation plus two of the following risk factors: age**≥75**, history of hypertension, diabetes, moderately or severely impaired left ventricular systolic function and/or heart failure (and no history of stroke). CHADS2 risk score = 2 *(see CHADS2 table, below)*.	3.7	Treat with anticoagulant (dabigatran or warfarin, as noted above)	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)
	• 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[39]	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8);
	• 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	If on warfarin, LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)
	• Aortic tissue valve up to three months after replacement	--	Either aspirin 325 mg daily or warfarin at INR target 2.0-3.0, per cardiac surgeon's preference	Use aspirin, not LMWH/Fondaparinux, if anticoagulated and INR becomes subtherapeutic**.**
	• Aortic or mitral tissue valve (>3 months after placement)	<4	Treat with aspirin 81-325 mg daily	Does not apply
	• Bileaflet mechanical aortic valve prosthesis without AF, prior stroke or TIA, hypertension, diabetes, congestive heart failure, or age ≥75yr)	<4	Treat with warfarin	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR
MODERATE RISK of Arterial Thromboembolic Event (consultation with AMS clinician generally required, unless previous	• Atrial fibrillation plus 3-4 of the following risk factors: age **≥75**, history of hypertension, diabetes, moderately or severely impaired left ventricular systolic function and/or heart failure (and no history of stroke); CHADS2 risk score = 3-4 *(see CHADS2 table, below)*.	6.2-7.2	Treat with warfarin	• Bridging LMWH recommended in many circumstances, especially if very low INR (below 1.4), expected hold ≥1 week, history of prior stroke, mechanical valve, rheumatic mitral valve disease with atrial fibrillation, or tissue aortic valve plus other significant risk factors. Bridging recommendation for a patient with CHADS2 score of 3-4 without history of stroke often depends on the specific risk
	• Atrial fibrillation with prior stroke, TIA or systemic embolization (not recent); CHADS2 risk score = 2-4, depending on other risk factors *(see CHADS2 table, below)*.	3.7-7.2		

[39] 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.

consultation has been completed and no clinical changes have occurred)[40]	• Bileaflet aortic mechanical valve and one of following risk factors: AF, prior stroke or TIA, hypertension, diabetes, CHF, age **≥75**	not quantified		factors, duration of low INR, presence or absence of antiplatelet agents, and personal preferences of the patient. • Note that perioperative risk of thromboembolic events substantially exceeds expected values based on CHADS2 figures, probably related to stimulation of the coagulation cascade by surgery. Therefore, when surgery is involved, the recommendation for bridging is stronger than in circumstances of an incidentally noted low INR value. • When bridging used, therapeutic LMWH suggested at therapeutic dose, since there is no available evidence to support prophylactic dosing for this purpose. However, prophylactic dose (30 mg SC bid or 40 mg SC qd) may be considered for short holds or in postoperative period when bleeding risk is high; aspirin 81 mg daily may be considered if LMWH not feasible or declined by patient. • For (1) prolonged (≥1 week) subtherapeutic (<1.8) INR, (2) expected hold (≥1 week or (3) any INR <1.4, LMWH 1 mg/kg bid or 1.5 mg/kg qd) is generally recommended until INR reaches therapeutic range.

[40] CHADS2 scores reflect risk of stroke in patients with nonvalvular atrial fibrillation based only on determinants CHF, hypertension, age and diabetes, each given 1 point, and history of TIA or stroke, 2 points. Use of the CHA(2)DS(2)-VASc schema may refine risk estimates for certain groups of patients, including women, older patients, and patients with documented vascular disease; see Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ; Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. This schema provides 1 point for age 65+ and an additional point for age 75+, 1 point for female gender, and 1 point for vascular disease (defined as PVD, prior MI, or aortic plaque), with possible total score of 9 compared to the 6 in the CHADS2 schema. It was not adopted in CHEST-9, though is commonly used in Europe.

HIGH RISK of Arterial Thromoboembolic Event (consultation with AMS clinician not required)	• All mechanical valves, first 3 months after placement.	≤40	Treat with warfarin	LMWH 1 mg/kg bid or 1.5 mg/kg qd while INR is subtherapeutic or prior to planned procedure, and resumed as soon as feasible based on post-operative bleeding risks. If full dose LMWH prohibited by bleeding risk during post-operative period, strongly consider prophylactic dose LMWH once hemostasis is secured.
	• Mitral bioprosthetic valves, first 3 months after placement. (Risk for mitral bioprosthetic valve higher than for aortic bioprosthetic valve, especially if history of systemic embolization or clot in left atrium, up to the first 12 months after placement)[41]	≤40		
	• History of stroke, TIA, or systemic embolization during first month post valve replacement	not quantified		
	• 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[42]		
	• Atrial fibrillation plus prior ischemic stroke, TIA, or systemic embolism within 3 months	not quantified		
	• *Atrial fibrillation with CHADS2 risk score of 5 or 6 (see CHADS2 table, below)*	33.3		
	• 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		
HIGHEST RISK of Arterial Thromboembolic Event (consultation with AMS clinician not required)	• Multiple St Jude's (or other mechanical valves)	91	Treat with warfarin	LMWH 1 mg/kg bid or 1.5 mg/kg qd) while INR is subtherapeutic or prior to planned procedure. Resume after procedure when cleared by surgeon. If full dose LMWH prohibited by bleeding risk during post-operative period, strongly consider prophylactic dose LMWH once hemostasis is secured.

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>:

- 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 criteria, understanding that they have been quantified only for nonvalvular atrial fibrillation) and prevailing clinical circumstances.

[41] 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.

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

CHADS2 Risk Factors and Score[43]:

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[44]	+2

Score	Risk of a Stroke
0-2	low
3-5	medium
6	high

Score	NRAF Adjusted Stroke Rate (95% CI)[45]	Estimated % with stroke at 1 year untreated[46]	Estimated % with stroke at 1 year treated with aspirin[47]	Estimated % with stroke at 1 year treated with warfarin[48]	Estimated % with stroke in 2 weeks untreated[49]	Estimated prevented strokes/1000 patients/2 weeks[50]
0	1.9 (1.2-3.0)	1.9	1.5	0.95	0.073	0.37
1	2.8 (2.0-3.8)	2.8	2.2	1.40	0.107	0.50
2	4.0 (3.1-5.1)	4.0	3.2	2.00	0.154	0.75
3	5.9 (4.6-7.3)	5.9	4.7	2.95	0.226	1.13
4	8.5 (6.3-11.1)	8.5	6.8	4.25	0.327	1.64
5	12.5 (8.2-17.5)	12.5	10.0	6.25	0.480	2.40
6	18.2 (10.5-27.4)	18.2	14.6	9.10	0.692	3.46

[43] 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

[44] 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 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).

[45] adjusted stroke rate/100 patient years from exponential survival model, assuming aspirin, assuming no aspirin or anticoagulation

[46] Estimate based on original CHADS2 study population, which used outcome measure at 1.2 years. These figures are provided for approximate estimation of patient risk during periods of subtherapeutic anticoagulation, and presume that patient risk is uniform over the study period, which may or may not be the case. Patients' actual risk level may depend on many other factors, including the actual INR values, clinical circumstances, and risk factors not evaluated in the study. Use of these figures to determine patient risk should never replace clinical judgment related to the actual medical condition of the patient. In addition, note that mathematical models based on long-term data collection always underestimate actual stroke risk during periods of increased coagulability such as the perioperative period.

[47] assumes 20% reduction in stroke with aspirin

[48] assumes 50% reduction of stroke with warfarin

[49] Based on percent at one year divided by 26.

[50] Based on presumption that therapeutic anticoagulation will reduce number of strokes by at least 50%; these figures may be helpful in providing concrete information to patients during decision to bridge during expected or existing periods of subtherapeutic anticoagulation.

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Appendix 7: General Recommendations for Perioperative Anticoagulation[51]

Principles of management

1. Most patients who require a hold of VKA 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 VKA should restart warfarin 12 to 24 hours after surgery, assuming there is adequate hemostasis.
3. Patients with mechanical heart valves, atrial fibrillation, or VTE at high risk of thromboembolism should be bridged with LMWH when VKA is held. Patients with mechanical heart valves, atrial fibrillation, or VTE at low risk of thromboembolism should not be bridged with LMWH when VKA is held. Patients 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.
4. Minor dental procedures, minor dermatologic procedures, and uncomplicated cataract surgery can usually proceed at therapeutic INR in the 2.0-3.0 range.
5. In most situations, patients receiving aspirin for secondary prevention of cardiovascular disease should continue aspirin rather than holding asprin for 7-10 days prior to the procedure.
6. Patients receiving therapeutic LMWH for bridging should receive the last dose approximately 24 hours before the procedure.
7. 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 (including extraction). Accordingly, CHEST guidelines state that warfarin should not be stopped for dental procedures except in a small percentage of patients considered at high risk for serious bleeding. Use local measures to control bleeding (pressure or 5% aminocaproic acid mouthwash, generally prescribed by dentist). For specific procedure recommendations, please consult the following sites: http://uwmcacc.org/pdf/dental.pdf (University of Washington Medical Center Anticoagulation Clinic) and http://www.med.umich.edu/cvc/prof/anticoag/dental.htm (University of Michigan Cardiovascular Center Anticoagulation Service for Health Professionals
   - **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

[51] Recommendations are based on Gould, M et al. Prevention of VTE in Nonorthopedic Surgical Patients - Prevention of VTE in Nonorthopedic Surgery Patients: 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.

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 HVMA 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** (e.g. cataract operations with glaucoma surgery[52], upper endoscopy or colonoscopy with excisional biopsy, extensive dermatologic surgery, cardiac catheterization, insertion of pacemakers, defibrillators, prosthetic joints, and GU or biliary stents): **hold for 5 days** before surgery (when INR >3.0, warfarin may need to be held for 6-7 days before surgery), to attain an INR of 1.5 or less on the day prior to surgery. If INR is above 1.5 on day prior to surgery, and surgery cannot be postponed, consider either ¼ of vitamin K 5.0 mg oral tablet (Mephyton 5 mg), or 1 mg Aquamephyton IV solution taken orally, since 1 mg oral tablets are not readily available. Unless INR is extremely close to 1.5 before administration of vitamin K, INR should be repeated before surgery. **Assess thromobembolic risk and use bridging with LMWH when required.**
4. For **Very high bleed risk procedures** (e.g. spinal surgery and epidural injections, and some urologic, orthopedic, and cardiac procedures), hold warfarin for 7 days to achieve INR of 1.2 or below on the day before surgery. If INR is above 1.2, consider either ¼ of vitamin K 5.0 mg oral tablet (Mephyton 5 mg), ten vitamin K1 100 mcg tablets (over-the-counter) or 1 mg Aquamephyton IV solution taken orally, since 1 mg oral tablets are not readily available. INR should be repeated before procedure.

[52] For specific HVMA ophthalmology parameters, refer to Eye Surgery Anticoagulation Parameters (HVMA).

Risk Assessment for GI Procedures

Procedure 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 • Pneumatic or bougie dilation • PEG placement • Endosonographic guided fine needle aspiration • Laser ablation and coagulation • Treatment of varices	• Diagnostic 1. EGD ± biopsy 2. Flex sig ± biopsy 3. Colonoscopy ± biopsy • ERCP without sphincterotomy • Biliary/pancreatic stent without endoscopic sphincterotomy • Endosonography without fine needle aspiration • Enteroscopy

Modified from American Society of Gastrointestinal Endoscopy: Guideline on the management of Anticoagulation and Antiplatelet Therapy for Endoscopic Procedures; volume 55, number 7, 2002; page 777; updated to reflect CHEST-9 guidelines

Surgeries That Will Usually Be Performed on Warfarin:

Dental • Restorations • Endodontics • Prosthetics • Uncomplicated extractions • Dental hygiene treatment • Peridontal therapy **Ophthalmologic** • Cataract extractions **Dermatologic** • Mohs micrographic surgery • Simple excisions and repairs	**GI** • Upper endoscopy *without* biopsy • Flexible sigmoidoscopy *without* biopsy • Colonoscopy *without* biopsy • ERCP *without* sphincterotomy • Biliary stent insertion *without* sphincterotomy - *maybe* • Endosonography *without* fine-needle aspiration • Push enteroscopy of the small bowel ***→ Review plan with the gastroenterologist before the procedure!*** **Orthopedic** • Joint aspiration • Soft tissue injections • Minor podiatric procedures

Modified from MA Coalition's presentation at the National Patient Safety Foundation Congress, May, 2008

Does patient require a "bridge"?

Suggested Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism			
	Indication for VKA Therapy		
	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**	• **CHADS2 score of 5 or 6** • **Recent (within 3 months) stroke or transient ischemic attack,** • **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**	• **CHADS2 score of 3 or 4**	• **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**	• **CHADS2 score of 0 to 2 (and no prior stroke or transient ischemic attack)**	• **Single VTE occurred >12 months ago and no other risk factors**

*High-risk patients may also include those with a prior stroke or transient ischemic attack occurring >3 months before the planned surgery with a CHADS2 score of <5, those with prior thromboembolism during temporary interruption of VKAs, 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)

From: The Perioperative Management of Antithrombotic Therapy; CHEST/141/2/February, 2012 Supplement; page 330S

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 all situations requiring interruption of anticoagulation, regardless of duration of the interuption or cause of the interuption. 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 require bridging when interuption 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. Bridging should be with therapeutic-dose LMWH, although low dose LMWH may be acceptable under some circumstances, such as an anticipated short period of interuption of VKA 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 the AMS physician 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 <u>therapeutic dose</u> 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 <u>prophylactic dose</u> 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 1.5 times usual daily dose for first two days, then decreasing to usual dose. Check INR 3-4 days after warfarin restart.
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 prophylatic LMWH 24 hours after the procedure once hemostasis is secured, and resumetherapeutic 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, Vitamin K 1 mg (Aquamephyton solution taken orally) or ten 100 mcg vitamin K1 tablets (over-the-counter) to1.25 mg (1/4 of 5 mg 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 involve epidural anesthesia or steroid injection, or other procedure requiring INR of 1.2 or less on day prior to procedure:

- 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, Vitamin K 1 mg (Aquamephyton solution taken orally) or ten 100 mcg vitamin K1 tablets (over-the-counter) to1.25 mg (1/4 of 5 mg 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.

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- **In all cases, timing of resumption of LMWH should be cleared by surgeon or other clinician (e.g. cardiologist implanting pacemaker or AICD ir 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 hemostais 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

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

Procedure	Options for anticoagulation	Comments
Elective THR and TKA	**Option 1:** LMWH (preferred) – 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].	• 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.*[53] • 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) 2.5 mg/day started 6-8 hours after surgery (not FDA-approved)	
	Option 3: Apixaban (Eliquis) - 2.5 mg orally twice daily started 12 to 24 hours after closure of the surgical wound;	
	Option 4: Dabigatran (Pradaxa) – 150 mg once daily, starting with a half-dose 1-4 h after surgery (not FDA-approved for this indication)	
	Option 5: Rivaroxaban (Xarelto) – 10 mg daily at least 6-10 hours after surgery once hemostasis has been established	
	Option 6: LDUH – 5000 units every 8 to 12 hours	
	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)[54]	
	Option 8: Aspirin ~160 mg daily	
	Option 9: Intermittent pneumatic compression device (IPCD)	
HFS (hip fracture surgery)	**Option 1:** LMWH (preferred) 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].	• 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. • See above comment regarding use of aspirin for VTE prophylaxis. • Although not in CHEST guidelines, it is
	Option 2: Fondaparinux (Arixtra) 2.5 mg/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)[55]	
	Option 4: LDUH – 5000 units every 8 to 12 hours	
	Option 5: Aspirin ~160 mg daily	

[53] Direct quote from Chest-2012-Falck-Ytter-Prevention of VTE in Orthopedic Surgery Patients – e290S.
[54] 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.
[55] Ibid.

	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)[56]	reasonable to consider treating first with LMWH followed by dose-adjusted warfarin or aspirin.
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) 30mg bid or 40mg 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) 2.5 mg/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)[57]	
	Option 4: LDUH – LDUH – 5000 units every 8 to 12 hours	
	Option 5: Aspirin ~160 mg 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)[58]	

Anticoagulation Management Responsibilities for Orthopedic Patients Receiving VTE Prophylaxis:

1. **The Anticoagulation Management Service will assume the responsibility for management of anticoagulation for all patients treated with warfarin, with or without the use of other anticoagulation and antiplatelet therapy. When management only includes other anticoagulants (such as LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, 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 VKA 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. **2.5 mg 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 (<2 mg) are being taken at the time of discharge.

[56] Ibid.
[57] Ibid.
[58] Ibid.

Hospital Discharge Procedures for the Orthopedist:

1. When VKA 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, 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, or enrollment will be deferred to the next business day.
2. Discharge notification must include:
   - Warfarin and/or LMWH/fondaparinux 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 Anticoagulation Management Service will assume responsibility for management on the day of discharge.
4. If information is missing or discharge notification is received after 4pm, the Anticoagulation Management Service will assume responsibility for management on the **next business day,** once complete information has been received.
5. In either case, the Anticoagulation 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 Anticoagulation manager will manage anticoagulation therapy in accordance with the patient's treatment plan and Anticoagulation Management Service guidelines.

Appendix 9: HYPERCOAGULABILITY EVALUATION [59] [60]

Definition of High Risk Thrombophilia:

1. In patients with at least one spontaneous event, high-risk thrombophilia is defined by the presence of antithrombin deficiency, antiphospholipid syndrome, or more than one single genetic defect (including heterozygous protein C, S or antithrombin deficiencies, as well as heterozygous Factor V Leiden or heterozygous prothrombin gene mutation combined with other significant thrombophilias).
2. Patients with one spontaneous event and low risk thrombophilia should now be considered high risk during certain clinical situations, such as surgery and in the setting of prolonged immobilization, including long plane flights.

Indications for Hypercoagulability workup (note; this evaluation should be completed by PCP or referring clinician, and will not be completed by AMS managers; information included for reference)[61]:

1. ***Suspected hypercoagulable conditions***:
   - First VTE at young age, any cause and any location
   - Recurrent VTE, any cause and any location
   - VTE with relevant family history (for example, first degree relative with history of VTE)
   - History of still birth fetus and contemplating another pregnancy
   - History of three or more unexplained spontaneous abortions and contemplating another pregnancy
   - Spontaneous VTE
   - VTE in unusual location (upper extremity vein in the absence of catheter or other trauma, mesenteric vein, or cerebral vein)

2. ***Consideration of stopping anticoagulation after acute treatment of DVT or PE of undetermined cause***. The presence of thrombophilia may be the deciding factor in the decision *to stop therapy after three to six months vs. to continue treatment on an extended basis*, which should be considered for all patients with unprovoked proximal DVT or PE. Sometimes the relative weight of bleeding vs. clotting risks will not be decisive. When bleeding risk is low or moderate, nearly all patients with significant thrombophilia will benefit from extended therapy. When bleeding risk is high, the risk of clotting may still outweigh the risk of bleeding if bleeding can be prevented or easily controlled. Appendix 1: Duration of Anticoagulation after Unprovoked DVT/PE..

3. ***Need for determination of use of LMWH for bridging in patients with DVT of undetermined cause receiving extended treatment*.** In these cases, presence of a high-risk thrombophilia may alter consideration of bridging when INR is low or expected to be low around the time of a procedure. As above, testing for antiphospholipid antibodies, Factor V R506Q Leiden, and activity of antithrombin, protein C, protein S, and prothrombin gene mutation (noted in **bold** below) should be considered. 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 patient assessments.

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[59] Chest-2012-Kearon-Antithrombotic Therapy for VTE Disease - e419S-92
[60] Review article with case presentations: Hypercoagulability: Too Many Tests, Too Much Conflicting Data; Bauer, KA, Rosendaal, FR, Heit, JA; Hematology: 2002; 1:353-368
[61] Bauer, KA. The Thrombophilias: Well-defined Risk Factors with Uncertain Therapeutic Implications. Annals of Internal Medicine. 1001; 135(5):367-73.

4. ***Concern with accuracy of ISTAT and other capillary point of care tests:*** The presence of lupus anticoagulant, anti-cardiolipin 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.
5. ***Need for determination of appropriate management in high-risk situations such as surgery or active cancer.***
6. ***Consideration of use of LMWH for bridging during periods of subtherapeutic anticoagulation in certain patients already designated for extended therapy.*** The additional presence of a significant thrombophilia may tip the balance in favor of bridging in these situations.

Other issues:

1. 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.[62]
2. 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.[63]
3. 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.[64]

Evaluation:

Note: testing for antiphospholipid antibodies, Factor V R506Q Leiden, and activity of antithrombin, protein C, protein S, and prothrombin gene mutation (noted in **bold** below) should be considered in appropriate clinical situations. 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 patient assessments.

[62] 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

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

[64] Bernas BL , Erkan D, Schur PH, Pisetsky DS, Romain PL; Diagnosis of the antiphospholipid syndrome; UpToDate; Feb 25, 2012.

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Specific tests:

Test	Is test reliable on warfarin?	Is test reliable on heparin?	Indications:	Comments:
ANTI CARDIOLIPIN ANTIBODY IgG/IgM [86147D]	Yes	Yes	Order all three in presence of: • one or more otherwise unexplained thrombotic or thromboembolic events; in cases of arterial thrombosis, additional workup may not be indicated • certain specific adverse outcomes related to pregnancy • otherwise unexplained thrombocytopenia or prolonged aPTT[65] Confirm positive tests after 12 weeks.	Can be done while patient on either warfarin or heparin.
ANTI BETA-2-GLYCOPROTEIN I ANTIBODY IgG/IgM [86146E]	Yes	Yes		Can be done while patient on either warfarin or heparin.
LUPUS ANTICOAGULANT EVALUATION W/REFLEX (FUNCTIONAL ASSAY) [85613A]	*Yes, if INR <3.5*	*No on UFH Yes on LMWH with anti-Xa therapeutic*		Best general screen for anti-phospholipid antibodies available at UMass Lab; includes Lupus Anticoagulant Screen, Hexagonal Phospholipid Confirm, DRVVT screen, and DRVVT 1:1 mix, with interpretation in the result Comments.
ANTITHROMBIN III TEST % [85301A]	Yes	No	Order for: • young (<age 50) patient with unexplained VTE or recurrent VTE (explained or unexplained) • VTE in presence of strong family history of VTE • VTE with FH of antithrombin III deficiency	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.
FACTOR V R506Q LEIDEN [83890H]	Yes	Yes	Order for: • any patient with unexplained VTE or recurrent VTE (explained or unexplained) • VTE in presence of strong family history of VTE • VTE with FH of factor V Leiden deficiency	Can be done while patient on either warfarin or heparin. More common in Caucasians than other racial groups.[66]
PROTEIN C ACTIVITY [85303C]	No*	Yes	Order for: • young (<age 50) patient with unexplained VTE or recurrent VTE (explained or unexplained) • VTE in presence of strong family history of VTE	*May be decreased by warfarin; if normal while patient is on warfarin, there is likely no deficiency. Factor V Leiden mutation may give falsely low values. Deficiency associated with warfarin-induced skin necrosis.

[65] Bermas, BL, Erkan, D, Schur, PH; Diagnosis of the antiphospholipid syndrome; UpToDate: Topic 4678 Version 9.0; Jul 26, 2012.

[66] 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.

			• VTE with FH of protein C deficiency	
PROTEIN S ACTIVITY [85306C]	No*	Yes	Order for: • young (<age 50) patient with unexplained VTE or recurrent VTE (explained or unexplained) • VTE in presence of strong family history of VTE • VTE with FH of Protein S deficiency	*May be decreased by warfarin; if normal while patient is on warfarin, there is likely no deficiency. Factor V Leiden mutation may give falsely low values. Deficiency associated with warfarin-induced skin necrosis.
PROTHROMBIN GENE (20210A) MUTATION [83891H]	Yes	Yes	Order for: • any patient with unexplained VTE or recurrent VTE (explained or unexplained) • VTE in presence of strong family history of VTE • VTE with FH of prothrombin gene mutation.	Can be done while patient on either warfarin or heparin. Heterozygous state results in relatively low-risk thrombophilia, unless VFL or other thrombophilia present.[67]

[67] 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.

Appendix 10: apixaban (Eliquis), dabigatran (Pradaxa), and rivaroxaban (Xarelto)

Atrius formulary: Stroke prophylaxis in the presence of non-valvular atrial fibrillation: warfarin is preferred over apixaban (Eliquis), dabigatran (Pradaxa) and rivaroxaban (Xarelto) for most patients. VTE prophylaxis after joint replacement therapy: enoxaparin (generic Lovenox) is preferred over rivaroxaban. Warfarin and apixaban remain the only oral anticoagulants currently included in the Atrius formulary. Further experience with and approval of other new agents will likely result in formulary approval over time.[68]

Apixaban (Eliquis)

In December 2012, the FDA approved apixaban (Eliquis), an oral direct factor Xa inhibitor, for prevention stroke and systemic thromboembolism prevention in non-valvular atrial fibrillation.

Potential advantages over warfarin:
- Lack of need for monitoring.
- Increased efficacy of stroke and systemic emboli prevention in patients with non-valvular atrial fibrillation.
- Decreased risk of major bleeding, intracranial bleeding and a composite of bleeding of any type.
- Rapid anticoagulation, which may eliminate the need for bridge therapy.

Potential disadvantages:
- Need for twice daily dosing, which makes it more problematic for some non-compliant patients.
- Lack of an accurate test to determine patient compliance.
- Risk of periods of under-anticoagulation during times of transition to and from warfarin.
- Lack of studies in patients with CrCl <25mL/min.
- Lack of an antidote, i.e. a drug to reverse its anticoagulation effects in the presence of major bleeding.

Place in Therapy:
- Apixaban should be considered for patients with non-valvular atrial fibrillation for stroke and systemic embolism prevention who have failed warfarin therapy or when warfarin therapy has been deemed unsafe (e.g., drug interactions that cannot be managed by dose adjustments, patients who travel abroad and have difficulty obtaining INRs).
- At this time, apixaban should only be used in patients with non-valvular atrial fibrillation. Its use beyond the FDA labeled indication is not advised based upon current data and recommendations from the Atrius Health P&T consultants.
- Note that apixaban has substantially higher copay than warfarin and thus higher cost to patients, and may in some insurances cost more than other novel anticoagulants. The decision to place patients on apixaban depends on the balance between the patient risk factors, lifestyle issues, insurance coverage, and ability to sustain higher copays for what is generally a small decrease in unfavorable events. The cost to the health care facility, excluding downstream costs such as complication-related hospitalizations and unfavorable patient outcomes, generally exceeds the cost of providing warfarin and

[68] http://shareplace.atriushealth.org/clinical/clinpharm/ptdocs/Documents/Oral Anticoagulants for Atrial Fibrillation.pdf

its management with a centralized anticoagulation program. Decisions must include assessment of the underlying condition and patient preferences and resources, as well as potential complications of each management option.

Dosing:
- Prevention of stroke with non-valvular atrial fibrillation: 5 mg orally twice daily; reduce dose to 2.5 mg orally twice daily if two or more of the following criteria are present (Scr ≥ 1.5mg/dL, age ≥ 80 years, weight ≤ 60kg).
- Use of apixaban should be avoided in patients with a CrCl <25mL/min, since this patient population was excluded in both the ARISTOTLE and AVERROES trial.

Adverse Drug Events:
- Bleeding is the primary adverse effect of concern, especially since there is no reversal agent and apixaban cannot be removed by dialysis. However, in the ARISTOTLE trial apixaban was shown to have significantly less major bleeding, intracranial hemorrhage and a composite of bleeding of any type compared to warfarin.

Drug Interactions:
- Apixaban interacts with both strong 3A4 and P-glycoprotein inhibitors and inducers (e.g., ketoconazole) and inducers (e.g., carbamazepine).
- Co-administration with other anticoagulants and antiplatelet drugs (e.g. NSAIDS, aspirin, and clopidogrel) may cause an increased risk of bleeding.

Dabigatran (Pradaxa)

In October 2010, the FDA approved dabigatran (Pradaxa), an oral reversible and selective direct thrombin inhibitor, for prevention of stroke in patients with non-valvular atrial fibrillation.

Potential advantages over warfarin:
- Lack of need for monitoring.
- Increased efficacy of stroke and systemic emboli prevention in patients with non-valvular atrial fibrillation.
- Decreased risk of intracranial bleeding compared to warfarin (RE-LY study).
- Rapid anticoagulation, which may eliminate the need for bridge therapy.

Potential disadvantages:
- Higher rate of gastrointestinal side effects (gastritis symptoms in 35% of patients in major trials).
- Higher rate of severe hemorrhage in the elderly population (age 80 years and older).
- Need for twice-daily doses, potentially more problematic for some non-compliant patients.
- Lack of an accurate test to determine patient compliance.
- Risk of periods of under-anticoagulation during times of transition to and from warfarin.
- Higher rate of gastrointestinal bleeding in patients age 75 years and older.
- Possibly higher rate of myocardial infarctions.
- Minimal efficacy and safety data for the 75 mg dose.
- Lack of studies in patients with CrCl <30mL/min.

- Lack of an antidote, i.e. a drug to reverse its anticoagulation effects in the presence of major bleeding.

Place in Therapy
- Dabigatran has substantially higher copay than warfarin and thus higher cost to patients, and may in some insurances cost more than other novel anticoagulants. The decision to place patients on dabigatran depends on the balance between the patient risk factors, lifestyle issues, insurance coverage, and the ability to sustain higher copays for the benefit of lack of need for testing and perhaps a slightly lower rate of strokes compared to warfarin. The cost to the health care facility, excluding downstream costs such as complication-related hospitalizations and unfavorable patient outcomes, generally exceeds the cost of providing warfarin and its management in a centralized anticoagulation program. Decisions must include assessment of the underlying condition and patient preferences and resources, as well as potential complications of each management option.
- Dabigatran is currently non-formularly, less preferable than apixaban for patients considered appropriate for novel anticoagulant therapy. It has more potential side effects than apixaban, a higher rate of gastrointestinal bleeding than warfarin for patients age 75 years and older, and a higher rate of myocardial infarctions than warfarin. As a twice-daily medication, it has no compliance advantages over apixaban. It may be a favored option in the tiering of some insurances, so probably should be reserved for patients who meet all the criteria for novel anticoagulants and have insurances that favor dabigatran over apixaban.
- CHEST-2012 guidelines, written prior to the approval of rivaroxaban and apixaban for stroke prophylaxis in the presence of non-valvular atrial fibrillation, suggest use of dabigatran rather than warfarin for this indication. This suggestion (not recommendation) was based on the results of the RELY trial, which demonstrated that "dabigatran at a dose of 150 mg bid is associated with a statistically significant one-third reduction in nonfatal stroke, with no evidence of a difference in the risk of nonfatal major extracranial bleeding compared with warfarin."

Dosing:
- Stroke and systemic embolism prevention in non-valvular AF: 150 mg twice daily (in patients with CrCl≥30 mL/min).
- Dabigatran should be avoided in patients with a CrCl <30mL/min because this population was not studied in clinical trials.

Adverse Drug Events
- Gastritis was the leading cause of discontinuation within clinical trials of dabigatran.
- Bleeding is the primary adverse effect of concern, since no reversal agent is available at this time.
- Due to increased risk of severe hemorrhage in the elderly (age ≥ 80y/o), avoid use in this population.

Drug Interactions
- Dabigatran is a substrate of P-glycoprotein and therefore should be avoided with P-glycoprotein inhibitors (e.g., ketoconazole, amiodarone, verapamil, and quinidine) and inducers (e.g., rifampin).
- Avoid other anticoagulants and antiplatelet drugs (e.g. NSAIDS, aspirin, and clopidogrel) due to increased risk of bleeding.

The current Atrius formulary does not include dabigatran (Pradaxa) for prevention of stroke and systemic embolization in patients with non-valvular atrial fibrillation. When prescribing this medication, clinicians should provide the following document to patients: Dabigatran (Pradaxa) Guide for Patients: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Pradaxa/Patient+Info/PradaxaMedGuide.pdf.

Rivaroxaban (Xarelto)

In July 2011, the FDA approved rivaroxaban (Xarelto), an oral direct factor Xa inhibitor. Indications for use include:

- VTE prophylaxis post hip and knee arthroplasty.
- Treatment of DVT and PE.
- Reduction of risk for recurrent DVT and PE.
- Prevention of stroke and systemic thromboembolism in non-valvular atrial fibrillation.

An indication for use in acute coronary syndrome was rejected by the FDA due to problems with the clinical trials.

Potential advantages over warfarin and dabigatran:

- VTE prophylaxis- oral dosing versus subcutaneous dosing with enoxaparin (generic Lovenox) is more convenient, requires less teaching, and is less expensive than LMWH, even when generic enoxaparin is prescribed. Depending on insurance coverage, this cost benefit may or may not be passed on to the patient.
- No need for INR monitoring (compared to warfarin).
- Potentially less GI irritation than dabigatran, although not evaluated in head-to-head clinical trials (and probably never will be).

Disadvantages:

- Lack of an accurate test to determine patient compliance.
- Risk of periods of under-anticoagulation during times of transition to and from warfarin.
- Lack of superiority over warfarin for stroke prophylaxis – rivaroxaban was only found to be non-inferior to warfarin; both dabigatran and apixaban were found to be superior to warfarin.
- Transitioning to and from warfarin may increase risk of periods of under-anticoagulation; abrupt discontinuation of rivaroxaban has been associated with stroke in some atrial fibrillation patients.
- Lack of an antidote, i.e. a drug to reverse its anticoagulation effects in the presence of major bleeding; cannot remove by dialysis.

Place in therapy:

- VTE Prophylaxis after joint replacement surgery: Atrius Health and the CHEST-9 guidelines on antithrombotic therapy prefer enoxaparin (generic Lovenox) to rivaroxaban (Xarelto) for VTE prophylaxis due to a lack of long-term efficacy data with rivaroxaban and a trend towards increased major and minor bleeding in clinical trials. In four randomized, controlled clinical trials comparing rivaroxaban to subcutaneous enoxaparin after hip and knee replacement surgery, rivaroxaban 10mg daily orally was found to be superior in DVT prophylaxis, but similar to enoxaparin in pulmonary embolism and mortality outcomes.
- DVT/PE treatment: The Atrius P&T Committee prefers enoxaparin (generic Lovenox) to rivaroxaban (Xarelto) for the treatment of DVT/PE, though has yet reviewed rivaroxaban for the treatment of DVT/PE or the reduction in risk of recurrent DVT and PE. However, if used for the treatment of DVT/PE treatment, rivaroxaban should be dosed 15mg orally twice daily (with food) for three weeks, followed by 20mg orally once daily (with food) for the duration of the treatment. In general, the EINSTEIN-DVT and EINSTEIN-PE trials have shown that rivaroxaban has similar efficacy for DVT and PE treatment without an increased bleeding risk when compared to conventional anticoagulation therapy (enoxaparin plus warfarin). The EINSTEIN-DVT EXTENSION trial suggested that extended treatment with rivaroxaban was superior to placebo for the prevention of VTE following the conventional three months of

anticoagulation. However, extended therapy does come with an increased bleeding risk. Duration of therapy depends on the presence or absence of reversible contributing factors and the presence or absence of increased bleeding risk in situations requiring extended therapy (e.g. 3 months when DVT follows surgery and ≥3 months when unprovoked with duration dependent on bleeding risk). Rivaroxaban has not yet been adequately studied as an agent for use in the presence of documented hypercoagulability.

- Atrial Fibrillation: INR-adjusted warfarin remains the therapy of choice for AF within Atrius Health, with apixaban as a second-line option for specific patients, as noted above. CHEST-9 guidelines do not mention rivaroxaban with respect to the atrial fibrillation indication, since this drug was not yet available in the US market at the time of publication of these guidelines. In clinical trials, rivaroxaban 20mg daily (15mg daily for CrCl 30-49mL/min) was compared to warfarin to an INR target of 2.5 (2.0-3.0 range) in moderate to high risk AF patients. Although fewer patients experienced stroke or systemic embolism within the rivaroxaban group, analysis was only powered to detect non-inferiority to warfarin. The rate of major and non-minor clinically relevant bleeding was similar between groups. However, gastrointestinal bleeding, a drop in hemoglobin >2mg/dL, and need for transfusion occurred more commonly in the rivaroxaban group. Fatal bleeding or bleeding into a critical anatomical site occurred less commonly in the rivaroxaban group.

Dosing:

- VTE prophylaxis: 10 mg once daily for 12 days post-knee arthroplasty, 35 days post-hip arthroplasty.
- Prevention of stroke with nonvalvular atrial fibrillation: 20 mg once daily with evening meal; reduction to 15 mg daily recommended with EGFR 15-50.

Adverse Drug Events:

- Bleeding is the primary adverse effect of concern, especially since there is no reversal agent and cannot remove by dialysis.
- In the AF clinical trial, GI bleeding, drop in hemoglobin >2mg/dL, and need for transfusion occurred more commonly with rivaroxaban than warfarin; however, fatal bleeds and bleeds into a critical anatomical site were less frequently seen with rivaroxaban.

Drug Interactions:

- Rivaroxaban interacts with both strong 3A4 and P-glycoprotein inhibitors (e.g., ketoconazole) and inducers (e.g., carbamazepine).
- Avoid other anticoagulants and antiplatelet drugs (e.g. NSAIDS, aspirin, and clopidogrel) due to increased risk of bleeding.

Rivaroxaban was reviewed for *Formulary* consideration by the Atrius Health Pharmacy and Therapeutics (P&T) Committee; at the present time, this drug remains a third line non-formulary agent for both VTE prophylaxis and atrial fibrillation indications.[69]

[69] Xarelto - Atrius formulary review - 2012