

**Harvard Vanguard Medical Associates  
Anticoagulation Management Service  
CLINICAL GUIDELINE<sup>1</sup> AND PRACTICE PROTOCOL<sup>2</sup>**

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<sup>1</sup> 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.

<sup>2</sup> Adapted from Antithrombotic and Thrombolytic Therapy, 8<sup>th</sup> Edition: ACCP Guidelines; vol. 133/Number 6 supplement. For access online, go to: [http://chestjournal.chestpubs.org/content/133/6\\_suppl](http://chestjournal.chestpubs.org/content/133/6_suppl)  
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## INTRODUCTION

The Anticoagulation Management Service (AMS) complements care provided by Harvard Vanguard Medical Associates primary care and specialty clinicians by offering intensive monitoring and management of oral anticoagulation therapy. The AMS supports patient management through interventions including frequent monitoring and patient education.

The AMS is available to all patients who receive their primary care through the Harvard Vanguard Medical Associates Internal Medicine practice and who are referred to the service by their primary care physician or a collaborating prescribing clinician who is part of the HVMA practice.

Once enrolled, AMS assumes full responsibility for day-to-day management of patients' oral anticoagulation therapy. The service operates 24/7 through an on-call system, a relationship with Telecom and the Weekend Urgent Care Program. 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.

## REFERRAL AND ENROLLMENT

Steps in referral should include:

1. 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. Prior to initiating treatment, the referring clinician obtains a baseline INR, hemogram and creatinine, if unknown, 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, referencing Appendix 10 for hypercoagulability screening guidelines when this evaluation is needed. Note that any baseline INR >1.1 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, when required, should not be delayed, as accurate testing may be precluded once the patient has been fully anticoagulated (see [Appendix 10: Hypercoagulability Evaluation](#)).

3. 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](#).
4. 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), the AMS manager will insure that the patient receives these documents or similar documents available as SmartText within the EMR.

5. 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.
6. 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 “Anticoag” in EpicCare order screen), using specific indications as enumerated in [Appendix 1: Guideline for Establishing INR Goal and Duration of Treatment](#).
7. The Anticoagulation Management Service operates under an approved guideline (this document), created in accordance with CHEST-8 guidelines and other evidence –based anticoagulation literature. In general, 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 responsibility of the chief or physician consultant to respond on the same business day. Examples of cases that might well be considered reasonable though outside of guidelines include (1) 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, and (2) 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 (1) 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, (2) the use of target ranges including any values below 1.8 for prevention of stroke in patients with atrial fibrillation, and (3) 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. 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. 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. 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. 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.
  - enrollment in MyHealth with agreement to regularly access e-mail for result notification and dosing instructions.

Patients are advised that repeated unavailability to receive results and dosing instructions may result in disenrollment from the AMS.

### Patient Education

The AMS manager assesses the patients 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
- How warfarin affects clot formation
- The brand and generic names for warfarin, tablet sizes/colors/strengths, and importance of verifying tablet strength after each prescription fill/refill
- The need for regular blood tests (called prothrombin times, PT-Coumadin tests or INRs), frequency of testing, and what the tests measure
- The procedure for obtaining an INR test, 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) 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 stable values in targeted range 1.5-2.0 may reasonably defer tests to a maximum of 8 weeks, barring any instances of potential instability.**
- 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 managed 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)
- 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, 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 (in most situations, make up one or two missed doses as soon as discovered)
- Program operations, including phone number, hours of operation, emergency contact number, laboratory testing, notification of INR results, and other AMS procedures.

### **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. In some situations, use of vitamin K 100mcg daily as an over the counter supplement may be a reasonable consideration to help decrease variability of INR values, particularly when dietary vitamin K intake is low or erratic. The availability of this supplement also provides an option for rapid treatment of markedly elevated INR values, should they occur.

## 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 and letters after the patient's INR due date.

- **Patients who require frequent monitoring** (new starts, on Lovenox 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. The patient is contacted daily 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**, are contacted according to the following schedule:
  1. At 3-5 days after INR due date, the AMS secretary starts calling the patient at 2 to 3 day intervals.
  2. At 10 days after INR due date, the AMS secretary sends a letter to the patient's home requesting a call to the AMS service and a visit to the lab within two days.
  3. At 20 days overdue, the patient is notified by certified mail that he/she is overdue well beyond safe management standards and will be terminated (disenrolled) from the program and care returned to the PCP if appropriate follow-up has not occurred within 10 days. This step will only be taken after collaboration with the PCP, who will receive a copy of the letter.
  4. At 30 days overdue, after review with the chief or 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, CCd to the PCP.
- **Patients who are in stable management** (INRs monitored >2 weeks) are contacted according to the following schedule:
  1. At 7 days (one week) after INR due date, the AMS secretary starts calling the patient at 2 to 3 day intervals.
  2. At 14 days (two weeks) after INR due date, the AMS secretary sends a letter to the patient's home requesting a call to the AMS service and a visit to the lab within two days.
  3. At 28 days (4 weeks) overdue, the patient is notified by certified mail that he/she is overdue well beyond safe management standards and will be terminated (disenrolled) from the program and care returned to the PCP if appropriate follow-up has not occurred within 2 weeks. This letter will be copied to the PCP, who may also take steps to engage the patient at his/her discretion.
  4. At 42 days (6 weeks) overdue, after review with the chief or 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, CCd 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.

## APPENDIX

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

Indications	Goal INR Range	INR Target	Duration of Therapy/Comments
<b>Prophylaxis of DVT</b>			
<ul style="list-style-type: none"> <li>High risk surgery such as joint replacements</li> </ul>	Appendix 9	-	Options for prophylaxis include LMWH, fondaparinux, and warfarin; see details in Appendix 9
<ul style="list-style-type: none"> <li>High risk patients post-operative patients (obese, bedridden, cancer)</li> </ul>	2.0-3.0	2.5	Until resolution of high-risk condition
<ul style="list-style-type: none"> <li>Long distance travel&gt;8hours,plus additional risk factors for VTE</li> </ul>	N/A	N/A	Single prophylactic dose of LMWH prior to departure
<b>Treatment of DVT(applies to calf, proximal lower extremity or upper extremity) or pulmonary embolism</b>			
<ul style="list-style-type: none"> <li>Patients with high clinical suspicion of DVT/ PE awaiting diagnostic testing</li> </ul>	N/A	N/A	Begin treatment immediately with agent for initial therapy (see next row)
<ul style="list-style-type: none"> <li>1<sup>st</sup> episode of DVT/PE due to transient, reversible identifiable risk factor</li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>All patients should receive initial treatment with weight-based SC LMWH, weight-based unmonitored SC UFH, or SC fondaparinux for at least 5 days <b>and</b> until INR is <math>\geq 2.0</math> at least 24 hrs; warfarin should be started on day of initial treatment.</li> <li>3 months is minimum duration of treatment if identified underlying condition is already resolved or &gt;3 months until resolution of that condition.</li> </ul>
<ul style="list-style-type: none"> <li>1<sup>st</sup> episode, high risk of recurrent thrombosis due to identifiable risk factor that is likely to persist</li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>All patients should receive initial treatment with weight-based SC LMWH, weight-based unmonitored SC UFH, or SC fondaparinux for at least 5 days <b>and</b> until INR is <math>\geq 2.0</math> at least 24 hrs; warfarin should be started on day of initial treatment.</li> <li>Treatment duration indefinite, as long as identifiable risk factor persists</li> </ul>
<ul style="list-style-type: none"> <li>1<sup>st</sup> episode, patients with DVT/PE and cancer <b>in active treatment</b></li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>Consider LMWH or fondaparinux for entire duration of treatment; considered more effective than warfarin, which is acceptable alternative.</li> <li>If using warfarin, same considerations as noted in above box apply. Continue duration until oncologist considers patient no longer at risk.</li> </ul>
<ul style="list-style-type: none"> <li>1<sup>st</sup> episode without identifiable cause</li> </ul>	2.0-3.0	2.5	3 months (minimum duration) followed by risk

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			benefit evaluation for long-term therapy. Considerations: <ul style="list-style-type: none"> <li>If first isolated <u>distal</u> DVT, 3 months usually sufficient</li> <li>If first episode of <u>proximal</u> DVT with low bleeding risk, long-term treatment recommended</li> <li>If second such episode, long-term treatment recommended (after same assessment)</li> </ul> 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, <u>after at least 3 months</u> at standard intensity) <sup>3,4,5</sup>
<ul style="list-style-type: none"> <li>1<sup>st</sup> episode, high risk of recurrent thrombosis due to identifiable risk factor likely to persist</li> </ul>	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. <sup>6</sup>
<ul style="list-style-type: none"> <li>2<sup>nd</sup> episode, whether or not cause identifiable, if cause unknown or not resolved</li> </ul>	2.0-3.0	2.5	Lifetime (standard intensity 2.0-3.0 preferred; may consider low intensity 1.5-2.0 if increased bleeding risk or patient preference, <b>after 12 months</b> at standard intensity)
<ul style="list-style-type: none"> <li>Asymptomatic DVT (unexpected finding or serendipitously discovered) should be evaluated, treated initially and subsequently in the same way as symptomatic DVT/PE</li> </ul>	2.0-3.0	2.5	Use relevant criteria from above boxes.
<ul style="list-style-type: none"> <li>Upper extremity DVT</li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>Treatment protocol same as lower extremity DVT, using initial LMWH, IV UFH, or</li> </ul>

<sup>3</sup> 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>

<sup>4</sup> "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>

<sup>5</sup> 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>

<sup>6</sup> 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>

			<p>fondaparinux with 2 day overlap at therapeutic INR with warfarin, continued for no less than 3 months</p> <ul style="list-style-type: none"> <li>• If DVT associated with IV catheter and catheter still present and functioning, it does not need to be removed.</li> <li>• If DVT associated with IV catheter and catheter removed, still need treatment for no less than 3 months</li> <li>• Routine use of compression stockings or wraps not recommended unless at specific high risk for swelling.</li> </ul>
<ul style="list-style-type: none"> <li>• <b>DVT/PE while at therapeutic level of anticoagulation, without identifiable cause or with identifiable cause likely to persist</b></li> </ul>	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
<ul style="list-style-type: none"> <li>• <b>DV/PE while at therapeutic level of anticoagulation, with identifiable cause no longer present</b></li> </ul>	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.
<b>Thrombophilias and DVT</b>			
<ul style="list-style-type: none"> <li>• <b>1<sup>st</sup> or subsequent episode in the presence of high risk thrombophilia</b>, defined as: <ul style="list-style-type: none"> <li>a. One spontaneous event plus antiphospholipid syndrome, deficiency of anti-thrombin, protein C, or protein S, or multiple abnormalities</li> <li>b. Two or more spontaneous events plus all other causes of thrombophilia</li> <li>c. One spontaneous life threatening event, such as massive near fatal PE, cerebral, mesenteric or portal vein thrombosis</li> <li>d. One spontaneous event at unusual site, such as cerebral, mesenteric or portal vein thrombosis regardless of presence of genetic factor for thrombophilia</li> <li>e. One spontaneous event in usual site, such as DVT/PE, in setting of more than one genetic factor for thrombophilia</li> </ul> </li> </ul>	2.0-3.0	2.5	Lifetime (standard intensity 2.0-3.0); treatment phase 6-12 months and then prophylactic phase for lifetime (standard intensity unless clinical circumstances indicate otherwise)
<ul style="list-style-type: none"> <li>• <b>Lupus inhibitor with other risk factors or thromboembolic events while at therapeutic INR</b></li> </ul>	2.5-3.5	3.0	Lifetime
<ul style="list-style-type: none"> <li>• <b>Other inherited thrombophilias (see Appendix 10)</b></li> </ul>	2.0-3.0	2.5	<p>Initial treatment 6 to12 months; lifetime prophylaxis preferred, as in DVT/PE without identifiable cause, but mandatory only if</p> <ul style="list-style-type: none"> <li>• 2 or more spontaneous thromboses,</li> <li>• one spontaneous life-threatening thrombosis or thrombosis at unusual site,</li> <li>• one spontaneous thrombosis in presence of &gt;1 high-risk genetic defect.</li> </ul>

<b>Acute Myocardial infarction</b>			
<ul style="list-style-type: none"> <li>Post myocardial infarction</li> </ul>	2.0-3.0	2.5	Low bleeding risk (provides lower re-infarction rate and cardiovascular mortality for up to 4 years): <ul style="list-style-type: none"> <li>Anticoagulation with INR goal 2.0-3.0 plus aspirin 81mg daily.</li> </ul>
	2.5-3.5	3.0	<ul style="list-style-type: none"> <li>Anticoagulation with INR goal 2.5-3.5 without aspirin.</li> </ul>
	N/A	N/A	Moderate to high bleeding risk, or anticoagulation not advised for any other reason: <ul style="list-style-type: none"> <li>Aspirin 81mg daily with no anticoagulation.</li> </ul>
<ul style="list-style-type: none"> <li>Severe LV dysfunction (EF &lt; 30%), CHF, previous embolism, 2D-echo evidence of mural thrombosis, or AF (if transient or immediate post-MI period)</li> </ul>	2.0-3.0	2.5	3 months post-MI or until resolution of noted high-risk condition: <ul style="list-style-type: none"> <li>Anticoagulation with INR goal 2.0-3.0, in accordance with recommendation for high-risk condition, plus aspirin 81 mg.</li> </ul>
<ul style="list-style-type: none"> <li><b>Prevention of recurrent MI (if anti-platelet therapies cannot be used)</b></li> </ul>	2.5-3.5	3.0	Lifetime
<b>Atrial Fibrillation (AF) without valvular disease (includes paroxysmal and chronic AF and Atrial Flutter)<sup>7</sup></b>			
<ul style="list-style-type: none"> <li><b>Low risk for ischemic stroke, TIA or systemic embolism: lone AF/flutter</b> (no risk factors, age&lt;75, and no clinical or echocardiographic evidence of cardiomyopathy or valvular disease)</li> </ul>	N/A	N/A	Treat with aspirin 81-325 mg daily (only use warfarin if strong patient preference after risk-benefit discussion). <sup>8</sup>
<ul style="list-style-type: none"> <li><b>Intermediate risk for ischemic stroke, TIA or systemic embolism: AF/flutter with one moderate risk factor</b>, either diabetes, hypertension, moderate to poor systolic function), or age 75+</li> </ul>	2.0-3.0 if warfarin	2.5 if warfarin	Warfarin or aspirin 81-325 mg daily; warfarin preferred, though aspirin considered reasonable alternative depending on clinical circumstances and preferences of patient.
<ul style="list-style-type: none"> <li><b>High risk for ischemic stroke, TIA or systemic embolism: AF/flutter with history of previous TIA, ischemic stroke, or systemic embolism OR two or more moderate risk factors</b>, including diabetes, hypertension, moderate to poor systolic function), and age 75+</li> </ul>	2.0-3.0	2.5	Lifetime
<b>Atrial Fibrillation (AF) with valvular disease or prosthetic heart valve</b>			
<ul style="list-style-type: none"> <li><b>AF/flutter with rheumatic mitral valve disease</b></li> </ul>	2.0-3.0	2.5	Lifetime
<ul style="list-style-type: none"> <li><b>AF/flutter with bioprosthetic mitral and/or aortic heart valve</b></li> </ul>	2.0-3.0	2.5	Lifetime; <u>consider</u> addition of aspirin 81mg, 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.
<ul style="list-style-type: none"> <li><b>AF/flutter with mechanical low-risk aortic heart valve</b></li> </ul>	2.5-3.5	3.0	Lifetime
<ul style="list-style-type: none"> <li><b>AF/flutter with mechanical high-risk aortic heart valve or any mechanical</b></li> </ul>	2.5-3.5	3.0	Lifetime; <u>recommend</u> addition of aspirin 81mg

<sup>7</sup> All comments refer to persistent or paroxysmal AF/flutter, not to single episode due to reversible cause such as acute pulmonary infection.

<sup>8</sup> 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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<b>mitral valve</b>			unless patient at high risk of bleeding, such as in patients with history of GI bleed or >80 years of age.
<b>Atrial Fibrillation/flutter, duration of at least 48 hours or unknown, with planned electrical or pharmacologic cardioversion</b>			
<ul style="list-style-type: none"> <li><b>Option 1</b></li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>INR must be in therapeutic range (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.<sup>9</sup></li> <li>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 &gt; one prior episode of AF and risk factor status.</li> </ul>
<ul style="list-style-type: none"> <li><b>Option 2</b></li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>Immediate UFH with target PTT of 60, range 50-70s 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).</li> <li>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 &gt; one prior episode of AF, and risk factor status.</li> </ul>
<b>Atrial Fibrillation/flutter, duration &lt;48 hours, with planned electrical or pharmacologic cardioversion (also applies to emergency cardioversion with atrial fibrillation/flutter of any duration)</b>			
<ul style="list-style-type: none"> <li><b>Option 1</b></li> </ul>	N/A	N/A	<ul style="list-style-type: none"> <li>Immediate cardioversion without preceding anticoagulation (decision made during hospitalization)</li> </ul>
<ul style="list-style-type: none"> <li><b>Option 2</b></li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>Preferred if no contraindication to anticoagulation):</li> <li>Begin LMWH or UFH immediately (decision made during hospitalization)</li> </ul>

<sup>9</sup> 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.

			<ul style="list-style-type: none"> <li>Continue anticoagulation with warfarin at least 4 weeks after cardioversion regardless of risk factors.</li> </ul>
<b>Bioprosthetic (tissue) heart valves</b>			
<ul style="list-style-type: none"> <li><b>Aortic bioprosthetic (tissue) heart valves, first three months after replacement, no AF</b></li> </ul>	N/A	N/A	If no other indications for warfarin, aspirin 81mg daily recommended.
<ul style="list-style-type: none"> <li><b>Mitral bioprosthetic (tissue) heart valves, first three months after replacement, no AF</b></li> </ul>	2.0-3.0	2.5	<ul style="list-style-type: none"> <li>Warfarin preferred over aspirin; post-operative care includes use of IV UFH or SC LMWH/Fondaparinux until INR therapeutic</li> <li>If INR subtherapeutic during three month period, LMWH/Fondaparinux preferred over aspirin unless subtherapeutic period brief (i.e. no more than one week).</li> </ul>
<ul style="list-style-type: none"> <li><b>All bioprosthetic (tissue) heart valves, during the first three months post replacement, no AF but with history of systemic embolus prior to valve replacement</b></li> </ul>	2.0-3.0	2.5	Anticoagulation with warfarin for 3 months after valve replacement; then reassess based on other clinical issues noted above
<ul style="list-style-type: none"> <li><b>All bioprosthetic (tissue) heart valves, after first three months, no AF or history of systemic embolus</b></li> </ul>	N/A	N/A	Aspirin 81mg
<ul style="list-style-type: none"> <li><b>All bioprosthetic (tissue) heart valve + AF</b></li> </ul>	2.0-3.0	2.5	Lifetime; consider addition of aspirin 81mg, 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.
<ul style="list-style-type: none"> <li><b>All bioprosthetic (tissue) heart valve plus LV dysfunction, pacemaker, large LA, embolic stroke, or hypercoagulable state</b></li> </ul>	2.0-3.0	2.5	Lifetime
<b>Mechanical heart valves</b>			
<ul style="list-style-type: none"> <li><b>Aortic mechanical valves + no other risk factors</b> <ul style="list-style-type: none"> <li>Low risk (low thrombogenicity) valves <i>plus</i> normal sized atrium: bileaflet valves (St. Jude, Carbomedics) and tilting disc valves (Medtronic Hall tilting disc)</li> <li>Higher risk (higher thrombogenicity) valves: other tilting disk valves (Bjork-Shiley, Monostrut, Omniscience/Omnicarbon, Ultracor) and caged ball valves (Starr-Edwards)</li> </ul> </li> </ul>	2.0-3.0	2.5	Lifetime
	2.5-3.5	3.0	Add aspirin 81mg 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.
<ul style="list-style-type: none"> <li><b>All mechanical valves + risk factors, including AF, LV dysfunction, anterior-apical ST-segment elevation MI, LAE, low EF, or hypercoaguable state</b></li> </ul>	2.5-3.5	3.0	Add aspirin 81mg 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.
<ul style="list-style-type: none"> <li><b>All mechanical valves + history of systemic embolus despite a therapeutic INR</b></li> </ul>	2.5-3.5	3.0	Add aspirin 81mg 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.
<ul style="list-style-type: none"> <li><b>Aortic mechanical valve with target of 2.5 plus any mitral mechanical valve</b></li> </ul>	2.5-3.5	3.0	Lifetime
<ul style="list-style-type: none"> <li><b>Mitral mechanical valves: all types considered higher thrombogenicity</b></li> </ul>	2.5-3.5	3.0	Lifetime

<b>Valvular heart disease, all native valves</b>			
• <b>Mitral stenosis/insufficiency (rheumatic) with NSR and LA &lt;5.5</b>	N/A	N/A	No anticoagulation
• <b>Mitral stenosis/insufficiency (rheumatic) with NSR and LA ≥5.5</b>	2.0-3.0	2.5	Lifetime
• <b>Mitral stenosis/insufficiency (rheumatic) with AF. previous systemic embolism, or left atrial thrombus</b>	2.0-3.0	2.5	Lifetime; do not use concomitant anti-platelet agents unless systemic embolus at therapeutic INR
• <b>Mitral stenosis/insufficiency (rheumatic) with AF or history of systemic embolism while on oral anticoagulant at therapeutic range</b>	2.0-3.0	2.5	Lifetime; add aspirin 81mg or consider increase INR target range to 2.5-3.5.
• <b>Mitral valve disease and planned percutaneous valvotomy (PMBV) with LA thrombus present</b>	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.
• <b>Mitral valve prolapse (MVP) without associated risk</b>	N/A	N/A	No anticoagulation or antiplatelet agents indicated
• <b>MVP with history of TIA or stroke</b>	N/A	N/A	Aspirin 81mg daily
• <b>MVP with AF, documented systemic embolism, or recurrent TIAs despite aspirin therapy</b>	2.0-3.0	2.5	Lifetime
• <b>Mitral annular calcification (MAC) with no AF complicated by systemic embolism or TIA</b>	N/A	N/A	Aspirin 81mg daily. Consider warfarin if recurrent symptoms while on aspirin.
• <b>Mitral annular calcification with AF</b>	2.0-3.0	2.5	Lifetime
• <b>Aortic stenosis/insufficiency</b>	N/A	N/A	No anticoagulation
• <b>Aortic valve disease with annular calcification</b>	N/A	N/A	No anticoagulation or antiplatelet agents indicated
<b>Stroke: Secondary Prevention</b>			
• <b>Most patients with non-cardioembolic stroke or TIA (i.e. atherothrombotic, lacunar, or cryptogenic)</b>	N/A	N/A	Anti-platelet therapy, either aspirin, Aggrenox, or Plavix, recommended over anticoagulation
• <b>Non-cardioembolic stroke or TIA with well documented prothrombotic disorders</b>	2.0-3.0	2.5	Oral anticoagulation recommended over anti-platelet agents
• <b>Atrial fibrillation with recent stroke or TIA</b>	2.0-3.0	2.5	Lifetime, unless anticoagulation contraindicated; then anti-platelet agent
• <b>Cardioembolic stroke</b>	2.0-3.0	2.5	Lifetime, unless anticoagulation contraindicated; then anti-platelet agent
• <b>Stroke associated with aortic atherosclerotic lesions</b>	N/A	N/A	Anti-platelet agents recommended over no therapy
• <b>Stroke associated with mobile aortic thrombi</b>	2.0-3.0 if anticoagulated	2.5	Aspirin 81mg daily or anticoagulation with warfarin
• <b>Cryptogenic stroke associated with mobile aortic arch thrombi</b>	2.0-3.0	2.5	Either oral anticoagulation or anti-platelet agents
• <b>Cryptogenic stroke and PFO</b>	N/A	N/A	Aspirin 325 mg recommended over anticoagulation; use anticoagulation if another indication, such as DVT, AF, or hypercoagulable state, exists.
• <b>Cryptogenic stroke and PFO plus atrial septal aneurysm</b>	2.0-3.0 if anticoagulated	2.5	Aspirin 325mg daily or anticoagulation with warfarin; indications for treatment remain uncertain.
• <b>Mitral valve strands or prolapse with history of TIA or stroke</b>	N/A	N/A	Anti-platelet therapy
• <b>MVP with AF, documented systemic embolism, or recurrent TIAs despite aspirin therapy</b>	2.0-3.0	2.5	Lifetime

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<b>Post-partum anticoagulation</b>			
• <b>Post-partum after thrombotic event</b>	2.0-3.0	2.5	4-6 weeks (initially overlapped with UFH or LMWH/Fondaparinux until INR at least 2.0 on 2 consecutive days.)
• <b>Pregnant women with thrombophilia (other than antithrombin deficiency) and no prior VTE</b>	2.0-3.0	2.5	After delivery, use warfarin until risk related to pregnancy resolved, generally 4-6 weeks; considered safe for nursing mother.
<b>Pulmonary hypertension<sup>10</sup></b>			
• <b>Idiopathic pulmonary hypertension (confirmed by right heart catheterization)</b>	1.5-2.5	2.0	Anticoagulation part of core treatment due to increase in survival; duration = lifetime
• <b>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)</b>	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 epoprostenol are at additional risk due to potential for catheter-associated thrombosis, and should be anticoagulated in absence of contraindications.
• <b>Pulmonary hypertension due to thromboembolic disease</b>	2.0-3.0	2.5	Anticoagulation generally required for underlying condition, and presence of pulmonary hypertension further increases this indication.

<sup>10</sup> Medical Therapy for Pulmonary Arterial Hypertension; Chest 2004;126;38S-39S ([http://www.chestjournal.org/content/126/1\\_suppl/35S.full.html](http://www.chestjournal.org/content/126/1_suppl/35S.full.html))

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### **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, Omniscience/Omnicarbon, and Ultracor; they have INR target 3.0, range of 2.5-3.5.
  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

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

### Starting Doses and Adjustments

**Uncomplicated Patients** (All patients EXCEPT patients age 75 years old or greater, who are frail with multisystem disease, on drugs that increase potency of warfarin, have had prior at-goal treatment with low doses, or have known liver disease)

1. **Start therapy at 5mg (2 tabs of 2.5mg) daily for first 3 days**
2. **INR on day 4 and adjust dose as follows:**

- If INR 1.0-1.3, increase to 7.5mg qd
- If INR 1.4 -1.9, keep at 5mg qd
- If INR 2.0-2.9, decrease to 2.5mg qd
- If INR 3.0-3.4, decrease to 1.25mg qd
- If INR 3.5+, hold dose and decrease to 1.25mg qd

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.

**Patients Age 75 Years Old or Greater, Who Are 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 1.1**

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**

- |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"><li>1. INRs are monitored daily or every other day until the INR <math>\geq</math> 2.0 or as indicated by the referring physician.</li><li>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.</li><li>3. When the INR and dose of warfarin remain stable and therapeutic for one week, the INR will be checked weekly.</li><li>4. When the INR and dose of warfarin remain stable and therapeutic for three weeks, the INR will be checked in two weeks.</li><li>5. If the INR remains stable and therapeutic after these two weeks, the INR will be checked in one month.</li></ol> |
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## Appendix 3: GUIDELINES FOR MAINTENANCE DOSE ADJUSTMENT AND MONITORING

### 1- Guidelines to Maintain a Therapeutic INR Range of 2.0-3.0<sup>a</sup>

INR < 2.0 <sup>b</sup>	INR 3.1-3.7 <sup>c</sup>	INR 3.8-4.4 <sup>d</sup>	INR 4.5-5.0 <sup>d</sup>
↓ Increase weekly dose by 10%-20% ↓	↓ Decrease weekly dose by 10% to 20% ↓	↓ Hold dose for 1-2 days, then recheck 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 1 week of changed dose	Monitor INR within one week of changed dose

<sup>a</sup> If the INR is 2.0-3.0, the patient may be instructed to continue the same dose regimen, with a follow-up appointment within 2-4 weeks (2 weeks if dose recently changed and needs closer monitoring to ensure stability within therapeutic range).

<sup>b</sup> If the INR is 1.9 but had been therapeutic and stable on the present dose, manage as if the patient is at goal (see <sup>a</sup> above; repeat INR in 2 weeks). If the INR is < 1.9 but had previously been therapeutic and stable on the present dose regimen, first assess why INR is low. Maintain patient on current dose and check INR within one week if reason for low INR is identified through assessment and resolved (e.g. missed dose, more Vitamin K in diet, change in alcohol intake, interacting medication). If cause is missed dose(s), reasonable treatment may simply include replacement of missed dose(s) without change in dosing plan. If lab error is suspected (unusual with low INR values done by fingerstick), consider repeat of INR before making a change in the dosing plan, other than an interim "make-up" of a single day's dose.

<sup>c</sup> If the INR is 3.1 but had been therapeutic and stable on the present dose, manage as if the patient is at goal (see <sup>a</sup> above; repeat INR in 2 weeks). If the INR is > 3.1 but < 3.8 and had been therapeutic and stable on the present dose regimen, first assess reason for high INR. Maintain patient on current dose and check INR within one week if reason for high INR is identified through assessment and resolved (e.g. additional warfarin dose, less Vitamin K in diet, change in alcohol intake, interacting medication). If no identifiable cause or lab error is suspected, recheck INR before changing dose.

<sup>d</sup> If the INR is ≥ 3.8 but less than 5.0, whether or not there is an identifiable cause for the high INR, hold dose for 1-2 days and recheck INR before reducing dose. If lab error suspected, recheck INR same day or at latest one day after held dose.

<sup>e</sup> Note that high INR range values 4.0 and above done by fingerstick at HVMA labs will automatically be confirmed by a venous sample, and may sometimes vary up to a difference in 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.

### 2- Guidelines to Maintain a Therapeutic INR Range of 2.5-3.5<sup>e</sup>

INR < 2.5 <sup>f</sup>	INR 3.6-4.0 <sup>g</sup>	INR 4.1-4.5 <sup>h</sup>	INR 4.6-5.0 <sup>h</sup>
↓ Increase weekly dose by 10%-20% ↓	↓ Decrease weekly dose by 10%-20% ↓	↓ Hold dose for one day and recheck 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

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<sup>f</sup>If the INR is between 2.5 and 3.5, the patient may be instructed to continue the same dose regimen, with a follow-up INR within 2-4 weeks.

<sup>g</sup>If the INR is 2.4 but had been therapeutic and stable on the present dose, manage as if the patient is at goal (see <sup>f</sup> above; repeat INR in 2 weeks). If the INR is <2.4, but the INR had been in therapeutic range and stable on the present dose regimen, first assess why the INR is low. Maintain patient on current dose and check INR within one week if reason for low INR is identified through assessment and resolved (e.g. missed dose, more Vitamin K in diet, change in alcohol intake, interacting medication). If there is no identifiable cause or if lab error is suspected, recheck INR before changing dose.

<sup>h</sup>If the INR is 3.6 but had been therapeutic and stable on the present dose, manage as if the patient is at goal (see <sup>f</sup> above; repeat INR in 2 weeks). If the INR is >3.6, but the INR had been in therapeutic range and stable on the present dose regimen, first assess why the INR is high. Maintain patient on current dose and check INR within one week if reason for high INR is identified through assessment and resolved (e.g. additional Warfarin dose, less Vitamin K in diet, change in alcohol intake, interacting medication). If there is no identifiable cause or if lab error is suspected, recheck INR before changing dose.

<sup>i</sup>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 recheck INR before reducing dose. If lab error is suspected, recheck INR same day or at latest after one held dose.

<sup>j</sup>Note that high INR range values 4.0 and above done by fingerstick at HVMA labs will automatically be confirmed by a venous sample, and may sometimes vary up to a difference in 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.

**3-Guidelines to Maintain a Therapeutic INR Range of 1.5-2.0<sup>11</sup>**

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

**4-Guidelines to Maintain a Therapeutic INR Range of 1.8-2.3**

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.					

<sup>11</sup> 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.

### **5-INR Monitoring Standards for Patients on Maintenance Therapy**

1. Patients with indications other than “history of DVT/PE with no identifiable cause; target range 1.5-2.0” must 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 weeks, as long as results remain stable and in therapeutic range.
3. After a dose change, reassess:
  - Patients with non-therapeutic INRs who were *previously unstable* → in one week.
  - Patients with non-therapeutic INRs who were *previously stable* → in two weeks.

### **6-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.<sup>12</sup>
5. INR must be monitored repeatedly during Amiodarone starts and tapers, since this drug may have delayed effects.

### **7-INR Monitoring Standards for Pre-Cardioversion or Interrogation of AICDs with Threshold Testing<sup>13</sup>**

1. INRs are monitored weekly by AMS.
2. Doses are adjusted to maintain INR at least 2.0, aiming for target in high end of 2.0 to 3.0 range.
3. AMS manager reports any INR below 2.0 to cardiologist.
4. 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.
5. Assuming INR has been at least 2.0 for all weekly tests, at least three consecutive weeks (four weekly values):
  - CV will be performed at INR 2.0-4.2.
  - Cardiologist will make case by case decision for INR in range 4.2-5.0.
  - CV will be postponed at INR >5.0 – AMS manager will notify cardiologist to coordinate plan.

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<sup>12</sup> 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).

<sup>13</sup> If patient is having a simple interrogation without threshold testing (similar to interrogation of pacemaker), there are no anticoagulation requirements.

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6. Anticoagulation will continue at least 4 weeks after the procedure, to be discontinued on direction of the cardiologist. Monitoring during this time will follow usual testing guidelines, with bridging based on the CHADS2 or other relevant risk factors when and if required.

### **8-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 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.
  - If high risk indication that requires bridging (see Appendix 8), Lovenox 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 in range within the week prior to the procedure, which may proceed without holding warfarin or requiring a bridge with Lovenox. .
3. Post-operative 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 begin post-operative warfarin and LMWH (if indicated) after the procedure.
  - Except in unusual circumstances where hemostasis has not been maintained, patients may resume warfarin at usual dose the evening of the procedure.
  - 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 Lovenox 30mg bid or 40mg qd, (3) full dose Lovenox 1mg/kg bid or 1.5mg/kg qd, or (4) transition from prophylactic dose to full dose.
  - The AMS manager will discontinue Lovenox, if prescribed, once INR reaches therapeutic range.

## Appendix 4: GUIDELINE FOR INITIAL OUTPATIENT TREATMENT OF VENOUS THROMBOSIS AND PULMONARY EMBOLUS<sup>14</sup>

### 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
- e. HCG, if indicated

##### • **LMWH/Fondaparinux options:**

- a. Enoxaparin sodium (Lovenox) 1 mg/kg subcutaneously (sc) every 12 hours (if office or VNA visits are needed for LMWH, may use Lovenox 1.5 mg/kg qd as acceptable alternative)
- b. Fondaparinux
  - If patient weighs <50 kg, Fondaparinux 5 mg subcutaneously once a day
  - If patient weighs 50-100 kg, Fondaparinux 7.5 mg subcutaneously once a day
  - If patient weighs >100 kg, Fondaparinux 10 mg subcutaneously once a day

##### • **Warfarin prescriptions:** 2.5 mg tablets per protocol (see Appendix 2)

- If <75 years old, advise 5 mg (2 tablets) each night for 3<sup>15</sup> nights, then check morning INR
- If 75+ years old, advise 2.5 mg (1 tablet) each night for 2<sup>16</sup> 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.

<sup>14</sup> Adapted from CPAS Policy and Procedures, Kaiser Permanente Clinical Pharmacy Anticoagulation Service

<sup>15</sup> 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).

<sup>16</sup> If feasible, these patients should be checked on day 3 after 2 doses.

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 postphlebotic syndrome.**<sup>17</sup>

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<sup>17</sup> 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,

## Appendix 5: DOSE ADJUSTMENT PRINCIPLES:

**General Principles: overriding goal is to achieve day to day stability and steady state as quickly as possible.**

1. Only use one strength tablet and always start with 2.5 mg tablets, unless patient has previously been treated with either very low doses (e.g. 1mg daily) or very high doses (e.g.10+mg daily). The 2.5mg 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.
2. 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.
3. If on alternating schedule, assign the day for each dose; do not simply advise “alternate days.”
4. If on alternating schedule, do not use doses that differ by >50% (e.g. 3.75mg/5.0mg preferred, 2.5mg/5.0mg reasonable; 2.5mg/7.5mg not acceptable and should be recalculated).

***Assessment Prior to Dose Change: if dose change is needed, ask specific questions related to the issues below.***

AMS Anticoagulation Managers collect the following assessment information prior to any dose change:

1. Signs/symptoms of bleeding episodes (gingival bleeding, epistaxis, ecchymoses, hematuria, melena, blood per rectum, etc.).
2. Signs/symptoms of a thrombotic event (shortness of breath, pain/swelling of extremity, numbness, tingling, headache, etc.)
3. Signs/symptoms of drug intolerance (nausea, vomiting, diarrhea, rash, skin necrosis, etc.)
4. Changes in diet, use of alcohol, or physical activity (for example, restaurant dining, increase or decrease in vegetables, salads etc.).
5. Changes in concomitant drug therapy, especially:
  - OTC medications, especially cold pills, analgesics, and sleep remedies containing acetaminophen
  - Antibiotics
  - Anticonvulsants
  - Amiodarone
  - Corticosteroids
6. Compliance with prescribed anticoagulation regimen.
7. Interactions of relevant co-morbid diseases (CHF, thyroid, etc.).
8. Occurrence of factors that may contribute to increased risk of adverse event (i.e., recent injury, biopsies, trauma, and surgery).
9. Occurrence of recent hospitalization (planned or unplanned) or emergency department visits.
10. Upcoming invasive or endoscopic procedure with biopsy anticipated.
11. INR and other pertinent lab values.
12. Other relevant encounters and treatment plan changes.
13. Requirements for additional patient education or follow-up.

### **Things to consider when INR is high:**

1. Is patient taking correct dose? Ask what dose he/she is taking. Look at warfarin prescription in medication history

2. 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?**
3. Check to see if patient's medical condition has changed? Review office visits, urgent care visits, and telephone calls since last anticoagulation encounter. In particular, CHF, thyroid changes, and changes in liver function may affect the INR.
4. Has patient had any vomiting, diarrhea, or less intake in vitamin K foods within past 3 days? This will decrease the amount of vitamin K that the warfarin will have to work against.
5. Has the patient increased or decreased the amount of alcohol lately?
6. Consider lab error (as last resort) if INR is high for no apparent reason. If venous sample, ask patient if there were any problems while phlebotomist was drawing blood? If tube was not fully filled, then the anticoagulant in the tube may be diluting the blood and contributing to high INR.
7. If INR is high, what is the patient's bleeding risk?
  - Is patient currently experiencing any bleeding?
  - Has he/she had any bleeding in the past?

### ***Things to consider when INR is low:***

1. Is patient taking the correct dose? Have patient tell you what dose 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. If INR is low, 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.
  - Is subtherapeutic duration already or expected to be prolonged? If so, you may need to bridge with LMWH/Fondaparinux.

## Appendix 6: 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.
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. An elevated INR  $\geq 5.0$  but  $< 9.0$  **without significant bleeding** requires 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 200mcg - available OTC as 100mcg tabs), and close follow-up of the INR.

**In general, the consideration driving this decision for patients with INR  $\geq 5.0$  but  $< 9.0$  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), concurrent use of an antiplatelet agent, and/or prolongation of the high-INR state despite holding warfarin. When any of these conditions exists, more likely than not, the patient will need vitamin K. When all are absent, it is usually safe to simply hold warfarin and closely follow the INR.**

### Bleeding Risk Score:

Bleeding Risk Assessment Tool <sup>18</sup>	
Bleeding Risk Factors	Bleeding Risk Factor Points
Age $\geq 65$ years	1
History of Stroke	1
History of Gastrointestinal Bleed	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

<sup>18</sup> 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.

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3+	High
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## Application of Bleeding and Bleeding Risk Assessment to Clinical Scenarios<sup>19</sup>:

### Clinical Scenario 1: Patient is bleeding:

INR	Bleeding Risk Category	Guideline Plan:
Minor bleeding with INR $\geq$ 5.0	<i>All: critical actions</i>	<ul style="list-style-type: none"> <li>• <b>Notify AMS MD of INR and clinical description of bleeding.</b></li> <li>• <b>AMS MD advises clinical action if evaluation or other action required<sup>20</sup>.</b></li> <li>• <b>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.</b></li> </ul>
Serious and/or life-threatening bleeding, regardless of INR	<i>All: critical actions</i>	<ul style="list-style-type: none"> <li>• <b>Immediately contact PCP and send patient to emergency room.</b></li> <li>• <b>Notify AMS MD.</b></li> </ul>

### Clinical Scenario 2: Patient is not bleeding, but has INR 5.0-8.9:

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	<ul style="list-style-type: none"> <li>• <b>Immediately advise patient to take vitamin K 2.5mg and omit dose of warfarin. Vitamin K may be ordered by AMS manager in name of AMS MD.</b></li> <li>• <b>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.</b></li> <li>• <b>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.</b></li> <li>• <b>Therapy is resumed at a lower dose per protocol when the INR is within or approaching therapeutic range.</b></li> </ul>
Patient taking aspirin and/or other antiplatelet drug, and/or has had recent procedure that	Low or moderate risk	Absent	<ul style="list-style-type: none"> <li>• <b>Report indication/target range, INR, bleeding risk, presence of anti-platelet agent, and absence of other relevant clinical circumstances to AMS MD.</b></li> </ul>

<sup>19</sup> 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.**

<sup>20</sup> Examples of minor bleeding include lacerations with oozing that stops with pressure, nosebleed that stops quickly with pressure, blood to toilet paper. On site evaluation is recommended whenever bleeding is not obviously minor.

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would increase likelihood of bleeding			<ul style="list-style-type: none"> <li>• <b>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 200mcg (available OTC as 100mcg tabs).</b></li> <li>• Omit the next dose of warfarin.</li> <li>• Repeat INR next day; then reduce the weekly dose and resume treatment per protocol when INR is in or approaching therapeutic range.</li> </ul>
Patient taking aspirin and/or other antiplatelet drug, and/or has had recent procedure that would increase likelihood of bleeding	High risk	Absent	<ul style="list-style-type: none"> <li>• Immediately advise patient to take vitamin K 2.5mg and omit dose of warfarin. Vitamin K may be ordered by AMS manager in name of AMS MD.</li> <li>• <b>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.</b></li> <li>• 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.</li> <li>• Therapy is resumed at a lower dose per protocol when the INR is within or approaching therapeutic range.</li> </ul>
Patient <b>not</b> taking aspirin or other antiplatelet drug, with <b>no</b> recent procedure that would increase likelihood of bleeding	Low or moderate	INR <u>likely</u> to decrease with holding warfarin	<ul style="list-style-type: none"> <li>• Advise taking multivitamin, or preferably, if available, vitamin K 200mcg (available OTC as 100mcg tabs).</li> <li>• Omit next dose or two and monitor INR before making additional adjustments.</li> <li>• Resume therapy at lower dose when INR is in therapeutic range</li> <li>• Report to AMS MD not required.</li> </ul>
Patient <b>not</b> taking aspirin or other antiplatelet drug, with <b>no</b> recent procedure that would increase likelihood of bleeding	Low or moderate	INR <u>not likely</u> to decrease with holding warfarin	<ul style="list-style-type: none"> <li>• <b>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.</b></li> <li>• <b>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 200mcg (available OTC as 100mcg tabs).</b></li> <li>• Omit the next dose of warfarin.</li> <li>• Repeat INR next day; then reduce the weekly dose and resume treatment per protocol when INR is in or approaching therapeutic range.</li> </ul>
Patient <b>not</b> taking aspirin or other antiplatelet drug, with <b>no</b> recent procedure that would increase likelihood of bleeding	High	Present or absent	<ul style="list-style-type: none"> <li>• Immediately advise patient to take vitamin K 2.5mg and omit dose of warfarin. Vitamin K may be ordered by AMS manager in name of AMS MD.</li> <li>• <b>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.</b></li> <li>• 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.</li> </ul>

			<ul style="list-style-type: none"> <li>• Therapy is resumed at a lower dose per protocol when the INR is within or approaching therapeutic range.</li> </ul>
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**Clinical Scenario 3: Patient is not bleeding, but has INR ≥9.0:**

Clinical context	Bleeding Risk Score	Factors likely to interfere with INR returning to therapeutic range	Guideline Plan:
All	All	Present or absent	<ul style="list-style-type: none"> <li>• Immediately advise patient to take vitamin K 5mg 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 10mg 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.</li> <li>• Report intervention to AMS MD, who may recommend additional medical evaluation (if indicated, Anticoagulation Manager or PCP will make arrangements for obtaining this evaluation).</li> <li>• Notify PCP of high INR and above intervention.</li> <li>• 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.</li> <li>• Therapy is resumed at a lower dose per protocol when the INR is within therapeutic range.</li> </ul>

**Things to consider when INR is high:**

1. Is patient taking correct dose? Ask what dose he/she is taking. Look at warfarin prescription in medication history.
2. 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?
3. Check to see if patient’s medical condition has changed? Review office visits, urgent care visits, and telephone calls since last anticoagulation encounter. In particular, CHF, thyroid changes, and changes in liver function may affect the INR.
4. Has patient had any vomiting, diarrhea, or less intake in vitamin K foods within past 3 days? This will decrease the amount of vitamin K that the warfarin will have to work against.
5. Has the patient increased or decreased the amount of alcohol lately?
6. Consider lab error (as last resort) if INR is high for no apparent reason. Ask patient if there were any problems while phlebotomist was drawing blood? If venous sample and tube was not fully filled, then the anticoagulant in the tube may be diluting the blood and contributing to high INR.
7. If INR is high, what is the patient’s bleeding risk?

- Is patient currently experiencing any bleeding?
  - Has he/she had any bleeding in the past?
8. 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.

## Appendix 7: MANAGING PATIENTS WITH LOW INR VALUES

### **General Principles:**

1. The Anticoagulation Manager will assess patients for risk of an arterial thromboembolic event or DVT/PE
  - Prior to planned interruption of therapy for a scheduled procedure.
  - When INR is below 1.8 (unrelated to planned interruption in therapy) and below goal range.
2. If the treatment decision is not straightforward, the case is presented to the AMS MD for review. The AMS MD makes a treatment recommendation.
3. The Anticoagulation Manager notifies the PCP of the proposed treatment plan, including AMS MD recommendation if applicable.
4. When the patient requires treatment with LMWH/Fondaparinux in setting of **unplanned low INR**:
  - The PCP is responsible for placing LMWH/Fondaparinux orders, arranging for self-injection and lovenox teaching, and making alternative arrangements (daily office visits or home visit by visiting nurse) if the patient is unable to self-inject.
  - The Anticoagulation Manager discontinues LMWH/Fondaparinux once the INR is in therapeutic range.
  - When re-starting therapy, AMS managers should increase dose to 1.5 to 2 times usual dose for up to three days to more quickly bring INR back into range (and thus minimize the number of days receiving LMWH, if indicated). If dose increased, 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.
5. When the patient requires treatment with LMWH/Fondaparinux in setting of **planned low INR**, refer to **Appendix 8: General Recommendations for Perioperative Anticoagulation: When can anticoagulation restart?**

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

#### **Enoxaparin (Lovenox®):**

##### **Full Dose**

- Enoxaparin dose is weight-based at 1 mg/kg administered bid sc.
- While twice daily administration is preferred, LMWH can be dosed at 1.5mg/kg and administered once daily for patients who require visiting nurse or office visits for injection.

##### **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
- 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 30mg SC qd.
- Weight adjustment: less than 45 kg: consider reduced dosage, monitor anti-factor Xa if necessary

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- QD treatment doses for obese (>158 kg) patients are not advised.

**Dalteparin (Fragmin®):**

Condition	Dose
<b>Abdominal surgery (DVT prophylaxis):</b>	
• <i>Low to moderate DVT risk</i>	2500 IU 1-2 hours prior to surgery, then qd for 5-10 days postoperatively
• <i>High DVT risk</i>	5000 IU the evening prior to surgery and qd for 5-10 days postoperatively.
• <i>Malignancy</i>	2500 IU 1-2 hours prior to surgery and 12 hours later, then 5000 IU qd for 5-10 days postoperatively.
<b>Total hip surgery (DVT prophylaxis) options:</b>	<i>Note: delay post-op dosing until hemostasis is achieved.</i>
• <i>Postoperative start</i>	Initial: 2500 IU 4-8 hours after surgery. Maintenance: 5000 IU qd; start at least 6 hours after postsurgical dose
• <i>Preoperative (starting day of surgery):</i>	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
• <i>Preoperative (starting evening prior to surgery)</i>	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.
<b>Other indications:</b>	
<b>Unstable angina or non-Q-wave myocardial infarction:</b>	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.
<b>Venous thromboembolism (cancer patients):</b>	Initial (month 1): 200 IU/kg up to 18,000 IU qd for 30 days. Maintenance (months 2-6): ~150 IU/kg up to 18,000 IU qd. Note: if platelet count between 50,000-100,000/mm <sup>3</sup> , reduce dose by 2,500 IU until platelet count recovers to ≥100,000/mm <sup>3</sup> ; if platelet count <50,000/mm <sup>3</sup> , discontinue Dalteparin until platelet count recovers to >50,000/mm <sup>3</sup> . If EGFR <30, monitor anti-Xa levels to determine appropriate dose.
<b>Immobility/acute illness (DVT prophylaxis):</b>	5000 IU qd

Table adapted from DRUGDEX®

**Special considerations:**

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

**Fondaparinux (Arixtra®):**

**Full Dose**

- If patient weighs <50 kg, Fondaparinux 5 mg SC qd.

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- 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

<b>Thromboembolic Risk Assessment:<sup>21</sup></b>				
<b>Risk Category for arterial or venous thromboembolic event</b>	<b>Examples in risk category (note that some categories do not require anticoagulation, but are best treated with anti-platelet agents)</b>	<b>Yearly risk (%), if known</b>	<b>Recommendations for anti-thrombotic treatment</b>	<b>Recommendation for “bridge” for low INR, planned or unplanned (if unclear, consult AMS clinician; see note below<sup>22</sup>)</b>
<b>LOW RISK</b> of Arterial Thromboembolic Event (consultation with AMS clinician not required)	<ul style="list-style-type: none"> <li><b>Lone atrial fibrillation (no co-morbidities and age = &lt;75; CHADS-2 risk score = 0 (see below)</b></li> </ul>	1.4	Treat with aspirin 81 -- 325mg daily (only use warfarin if strong patient preference after risk-benefit discussion) <sup>23</sup>	If on warfarin, LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)
	<ul style="list-style-type: none"> <li><b>Atrial fibrillation plus only one of the following risk factors: age&gt;75, history of hypertension, diabetes, moderately or severely impaired left ventricular systolic function and/or heart failure (and no history of stroke). CHADS-2 risk score = 1 (see CHADS-2 table, below).</b></li> </ul>	3.1	Warfarin or aspirin 81-325 mg daily; warfarin preferred, though 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)
	<ul style="list-style-type: none"> <li><b>Atrial fibrillation plus two of the following risk factors: age&gt;75, history of hypertension, diabetes, moderately or severely impaired left ventricular systolic function and/or heart failure (and no history of stroke). CHADS-2 risk score = 2 (see CHADS-2 table, below).</b></li> </ul>	3.7	Treat with warfarin	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)
	<ul style="list-style-type: none"> <li><b>Cardiomyopathy without atrial fibrillation</b></li> </ul>	<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	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR (below 1.8)
	<ul style="list-style-type: none"> <li><b>Rheumatic mitral valve disease (stenosis and regurgitation; risk 1.5 times higher in stenosis) in absence of atrial fibrillation</b></li> </ul>	<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)

<sup>21</sup> 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 CHADS-2 data and CHEST-8 recommendations.

<sup>22</sup> 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 to the duration of interruption, and in general is decreased by about 50-67% by use of LMWH. The CHADS-2 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.

<sup>23</sup> 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.

	<ul style="list-style-type: none"> <li>• <b>Aortic tissue valve up to three months after replacement</b></li> </ul>	--	Either aspirin 325mg 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.
	<ul style="list-style-type: none"> <li>• <b>Aortic or mitral tissue valve (&gt;3 months after placement)</b></li> </ul>	<4	Treat with aspirin 81-100mg daily	Does not apply
	<ul style="list-style-type: none"> <li>• <b>Bileaflet mechanical aortic valve prosthesis without AF and no other risk factor for stroke</b></li> </ul>	<4	Treat with warfarin	LMWH not required when withholding oral anticoagulation for procedure or for other subtherapeutic INR
<b>LOW RISK</b> of Venous Thromboembolic Event (consultation with AMS clinician not required)	<ul style="list-style-type: none"> <li>• <b>DVT/PE &gt;12 months ago and no other risk factors</b></li> </ul>	<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.
	<ul style="list-style-type: none"> <li>• <b>Patients with heterozygous factor V Leiden mutation but no history of DVT/PE</b> (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)</li> </ul>			
	<ul style="list-style-type: none"> <li>• <b>Patients with heterozygous factor V Leiden mutation and history of DVT/PE &gt;12 months ago, no other predisposing issues</b> (risk of recurrence is virtually the same as the risk of recurrent DVT/PE when no predisposing factor has been found)</li> </ul>			
	<ul style="list-style-type: none"> <li>• <b>Patients anticoagulated due to pulmonary hypertension, in absence of history of thromboembolic disease</b> (if history of thromboembolic disease, risk generally relates to specific history of thromboembolic disease, not to the risk of pulmonary hypertension)</li> </ul>			
<b>MODERATE RISK</b> of Arterial Thromboembolic Event (consultation with AMS clinician generally required, unless previous	<ul style="list-style-type: none"> <li>• <b>Atrial fibrillation plus 3-4 of the following risk factors: age&gt;75, history of hypertension, diabetes, moderately or severely impaired left ventricular systolic function and/or heart failure (and no history of stroke); CHADS-2 risk score = 3-4 (see CHADS-2 table, below).</b></li> </ul>	6.2-7.2	Treat with warfarin	<ul style="list-style-type: none"> <li>• 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 CHADS-2 score of 3-4 without history of stroke often depends on the specific risk</li> </ul>
	<ul style="list-style-type: none"> <li>• <b>Atrial fibrillation with prior stroke, TIA or systemic embolization (not recent); CHADS-2 risk score = 2-4, depending on other risk factors (see CHADS-2 table, below).</b></li> </ul>	3.7-7.2		

<p>consultation has been completed and no clinical changes have occurred)<sup>24</sup></p>	<ul style="list-style-type: none"> <li>• <b>Bileaflet aortic mechanical valve and one of following risk factors: AF, prior stroke or TIA, hypertension, diabetes, CHF, age &gt;75</b></li> </ul>	<p>not quantified</p>		<p>factors, duration of low INR, presence or absence of antiplatelet agents, and personal preferences of the patient.</p> <ul style="list-style-type: none"> <li>• Note that perioperative risk of thromboembolic events substantially exceeds expected values based on CHADS-2 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.</li> <li>• For brief (&lt; one week) subtherapeutic INR or expected hold, consider LMWH at prophylactic dose (30 mg SC bid or 40 mg SC qd) or, if LMWH not feasible or declined by patient, aspirin 81mg daily.</li> <li>• For (1) prolonged (≥1 week) subtherapeutic (&lt;1.8) INR, (2) expected hold (≥1 week or (3) any INR &lt;1.4, LMWH 1mg/kg bid or 1.5mg/kg qd) is generally recommended until INR reaches therapeutic range.</li> </ul>
<p><b>MODERATE RISK</b> of Venous Thromboembolic Event (consultation with AMS clinician generally required, unless previous consultation has been completed and no clinical changes have occurred)</p>	<ul style="list-style-type: none"> <li>• <b>Brief subtherapeutic INR with history of DVT/PE in the setting of a therapeutic INR</b></li> <li>• <b>Brief subtherapeutic INR with history of DVT/PE in the setting of a hypercoagulable state, except as noted below under high risk thrombophilia</b></li> <li>• <b>A history of recurrent DVT/PE, due to specific condition no longer present</b></li> <li>• <b>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.</b></li> <li>• <b>DVT/PE with active cancer (treated within 6 months or palliative stage)</b></li> <li>• <b>DVT/PE 3 to 12 months</b></li> </ul>	<p>not quantified</p>	<p>Treat with warfarin</p>	<ul style="list-style-type: none"> <li>• 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)</li> <li>• 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, or even for the pre-operative period. In some circumstances, patients may need post-operative but not pre-operative bridging.</li> <li>• For brief (&lt; one week) subtherapeutic INR or expected hold, consider LMWH 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.</li> <li>• For prolonged (≥1 week) subtherapeutic INR or expected hold, or in some circumstances when INR &lt;1.4, use LMWH 1mg/kg bid or 1.5mg/kg qd) while INR is subtherapeutic.</li> </ul>

<sup>24</sup>CHADS-2 scores reflect risk of stroke in patients with nonvalvular atrial fibrillation based only on the bases of the determinants CHF, hypertension, age and diabetes, each given 1 point, and history of TIA or stroke, 2 points. Click on the following link for a detailed review of calculations based on CHADS-2 scores: [http://www.eboncall.org/JSP/GUIDE/atrial%20fibrillation/AF\\_prognosis.htm](http://www.eboncall.org/JSP/GUIDE/atrial%20fibrillation/AF_prognosis.htm). Since outcome measure in study was 1.2 years, noted yearly percent is approximated as 83.3% of study value.  
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<b>HIGH RISK</b> of Arterial Thromboembolic Event (consultation with AMS clinician not required)	<ul style="list-style-type: none"> <li>• <b>All mechanical valves, first 3 months after placement.</b></li> </ul>	≤40	Treat with warfarin	LMWH 1mg/kg bid or 1.5mg/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.
	<ul style="list-style-type: none"> <li>• <b>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)<sup>25</sup></b></li> </ul>	≤40		
	<ul style="list-style-type: none"> <li>• <b>History of stroke, TIA, or systemic embolization during first month post valve replacement</b></li> </ul>	not quantified		
	<ul style="list-style-type: none"> <li>• <b>Aortic caged ball (Starr-Edwards) or tilting disk (Bjork-Shiley) valve (valves with INR goal 2.5-3.5), regardless of additional risk factors</b></li> </ul>	not quantified		
	<ul style="list-style-type: none"> <li>• <b>Mechanical mitral valve; e.g. St. Jude bileaflet valve (with or without risk factor)</b></li> </ul>	~22 <sup>26</sup>		
	<ul style="list-style-type: none"> <li>• <b>Atrial fibrillation plus prior ischemic stroke, TIA, or systemic embolism within 3 months</b></li> </ul>	not quantified		
	<ul style="list-style-type: none"> <li>• <b><i>Atrial fibrillation with CHADS-2 risk score of 5 or 6 (see CHADS-2 table, below)</i></b></li> </ul>	33.3		
	<ul style="list-style-type: none"> <li>• <b>Atrial fibrillation with rheumatic valvular heart disease (especially mitral valve disease, particularly mitral stenosis)</b></li> </ul>	>10		
	<ul style="list-style-type: none"> <li>• <b>Any mechanical heart valve and recent (within 6 months) stroke or TIA</b></li> </ul>	>10		
<b>HIGH RISK</b> of Venous Thromboembolic Event (consultation with AMS clinician not required)	<ul style="list-style-type: none"> <li>• <b>DVT/PE within 3 months</b></li> </ul>	not quantified	Treat with warfarin	Postpone procedures requiring warfarin cessation when possible. Use LMWH 1mg/kg bid or 1.5mg/kg qd 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.
	<ul style="list-style-type: none"> <li>• <b>A prolonged subtherapeutic INR with history of DVT/PE in the setting of a therapeutic INR</b></li> </ul>	20+		
	<ul style="list-style-type: none"> <li>• <b>A prolonged subtherapeutic INR with history of DVT/PE in the setting of a hypercoagulable state</b></li> </ul>			
	<ul style="list-style-type: none"> <li>• <b>A history of recurrent DVT/PE, due to specific condition still present</b></li> </ul>			
	<ul style="list-style-type: none"> <li>• <b>High risk thrombophilia, defined as one of the following:</b> <ol style="list-style-type: none"> <li>• One spontaneous event plus <a href="#">antiphospholipid syndrome</a><sup>27</sup>, deficiency of antithrombin, protein C, or protein S, or multiple abnormalities</li> <li>• Two or more spontaneous events plus all other causes of thrombophilia except as in “a”</li> <li>• One spontaneous life threatening event like massive near fatal PE, or cerebral, mesenteric or portal vein thrombosis</li> <li>• One spontaneous event at unusual site, such as cerebral, mesenteric or portal vein regardless of presence of genetic factor for thrombophilia</li> <li>• One spontaneous in regular location and in setting of more than one genetic factor for thrombophilia</li> </ol> </li> </ul>			

<sup>25</sup> 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.

<sup>26</sup> Figure of 22% refers to annualized risk for St Jude bileaflet valve

<sup>27</sup> Anti-phospholipids include lupus anticoagulants, anticardiolipin antibody, and antiphospholipid antibody. See Appendix 10 for review.

	<ul style="list-style-type: none"> <li><b>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.</b></li> </ul>	not quantified		
<b>HIGHEST RISK</b> of Arterial Thromboembolic Event (consultation with AMS clinician not required)	<ul style="list-style-type: none"> <li><b>Multiple St Jude's (or other mechanical valves)</b></li> </ul>	91	Treat with warfarin	<b>LMWH 1mg/kg bid or 1.5mg/kg qd</b> 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, after the first three months following placement:**

- 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, CHADS-2 criteria, understanding that they have been quantified only for nonvalvular atrial fibrillation) and prevailing clinical circumstances.

**CHADS-2 Risk Factors and Score<sup>28</sup>:**

CHADS-2 Stroke Risk Factors	Score
Congestive heart failure	+1
Hypertension	+1
Age 75 years or older	+1
Diabetes mellitus	+1
History of stroke or TIA <sup>29</sup>	+2

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

Score	% with Stroke at 1.2 years	Estimated % with stroke at 1 year <sup>30</sup>	Estimated prevented strokes/1000 patients/year <sup>31</sup>	Estimated % with stroke in 1 week <sup>32</sup>	Estimated % with stroke in 2 weeks <sup>33</sup>	Estimated prevented strokes/1000 patients/2 weeks <sup>34</sup>
0	1.7	1.4	7	0.03	0.05	<1
1	3.7	3.1	16	0.06	0.12	<1
2	4.4	3.7	18	0.07	0.14	<1
3	7.4	6.2	31	0.12	0.24	1
4	8.6	7.2	36	0.14	0.28	1
5	9.2	7.7	39	0.15	0.29	2
6	40.0	33.3	167	0.64	1.28	6

<sup>28</sup> CHADS-2 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.

<sup>29</sup> 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 CHADS-2 criteria, but is logical since cardioembolic strokes presumably arise from these atrial clots. It is relevant for a reasonable period 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).

<sup>30</sup> Estimate based on 83.3% of values in CHADS-2 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.

<sup>31</sup> Based on presumption that therapeutic anticoagulation will reduce number of strokes by at least 50%.

<sup>32</sup> Based on percent at one year divided by 52.

<sup>33</sup> Based on percent at one year divided by 26.

<sup>34</sup> 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.



**Things to consider when INR is low:**

1. Is patient taking the correct dose? Have patient tell you what dose 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. If INR is low, 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.
  - Is subtherapeutic duration already or expected to be prolonged? If so, you may need to bridge with LMWH/Fondaparinux.

## Appendix 8: General Recommendations for Perioperative Anticoagulation<sup>35</sup>

### 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 websites: <http://jada.ada.org/cgi/reprint/128/3/327> (Journal of the American Dental Association, Vol 128, Issue 3, 327-335), <http://www.med.umich.edu/cvc/prof/anticoag/dental.htm> (University of Michigan Cardiovascular Center Anticoagulation Service for Health Professionals and <http://uwmcacc.org/pdf/dental.pdf> (University of Washington Medical Center Anticoagulation Clinic).
  - **Cataract operations:** For uncomplicated cataract surgery (i.e. not including complicated cataract surgery, such as concurrent glaucoma surgery), warfarin should generally not be stopped. However, all patients on anticoagulation who do not hold warfarin the last 4 days before surgery will have an INR drawn at MEEI prior to the procedure, and patients with an INR of above 3.0 may be cancelled. Therefore, we are requesting that all anticoagulation patients have an INR drawn within 7 days of surgery, with appropriate adjustments in management to insure that the INR will be  $\leq 3.0$  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 100mcg – 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.
  - **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, 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  $\frac{1}{4}$  of vitamin K 5.0mg oral tablet (Mephyton 5mg), or 1mg Aquamephyton IV solution taken orally, since 1mg 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 thromboembolic risk and use bridging with LMWH when required.**

<sup>35</sup> Recommendations are based on CHEST guidelines. Individual treatment decisions should be based on risk of bleeding vs. thromboembolism in individual patients.

**Risk Assessment for GI Procedures**

Procedure risk	Condition risk for Thromboembolism	
	High	Low
High	Discontinue warfarin 3-5 days before procedure. Consider heparin while INR is below therapeutic level.	Discontinue warfarin 3-5 days before procedure, dependent on most recent INR. Reinstate warfarin 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	
<ul style="list-style-type: none"> <li>• Polypectomy</li> <li>• Pneumatic or bougie dilation</li> <li>• PEG placement</li> <li>• Endosonographic guided fine needle aspiration</li> <li>• Laser ablation and coagulation</li> <li>• Treatment of varices</li> </ul>	<ul style="list-style-type: none"> <li>• Diagnostic               <ol style="list-style-type: none"> <li>1. EGD ± biopsy</li> <li>2. Flex sig ± biopsy</li> <li>3. Colonoscopy ± biopsy</li> </ol> </li> <li>• ERCP without sphincterotomy</li> <li>• Biliary/pancreatic stent without endoscopic sphincterotomy</li> <li>• Endosonography without fine needle aspiration</li> <li>• Enteroscopy</li> </ul>	

*Adapted 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*

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 5.0mg oral tablet (Mephyton 5mg), or 1mg Aquamephyton IV solution taken orally, since 1mg oral tablets are not readily available. INR should be repeated before procedure.

**Surgeries That Will Usually Be Performed on Warfarin:**

<p><b>Dental</b></p> <ul style="list-style-type: none"><li>• Restorations</li><li>• Endodontics</li><li>• Prosthetics</li><li>• Uncomplicated extractions</li><li>• Dental hygiene treatment</li><li>• Peridontal therapy</li></ul> <p><b>Ophthalmologic</b></p> <ul style="list-style-type: none"><li>• Cataract extractions</li></ul> <p><b>Dermatologic</b></p> <ul style="list-style-type: none"><li>• Mohs micrographic surgery</li><li>• Simple excisions and repairs</li></ul>	<p><b>GI</b></p> <ul style="list-style-type: none"><li>• Upper endoscopy <i>without</i> biopsy</li><li>• Flexible sigmoidoscopy <i>without</i> biopsy</li><li>• Colonoscopy <i>without</i> biopsy</li><li>• ERCP <i>without</i> sphincterotomy</li><li>• Biliary stent insertion <i>without</i> sphincterotomy - <i>maybe</i></li><li>• Endosonography <i>without</i> fine-needle aspiration</li><li>• Push enteroscopy of the small bowel</li></ul> <p><b>→ Review plan with the gastroenterologist before the procedure!</b></p> <p><b>Orthopedic</b></p> <ul style="list-style-type: none"><li>• Joint aspiration</li><li>• Soft tissue injections</li><li>• Minor podiatric procedures</li></ul>
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*Modified from MA Coalition's presentation at the National Patient Safety Foundation Congress, May, 2008*

**Does patient require a “bridge”?**

<b>Suggested Patient Risk Stratification for Perioperative Arterial or Venous Thromboembolism</b>			
<b>Indication for VKA Therapy</b>			
	<b>Mechanical Heart Valve</b>	<b>Atrial Fibrillation</b>	<b>VTE</b>
<b>High</b>	-Any mitral valve prosthesis -Older (caged-ball or tilting disc) aortic valve prosthesis -Recent (within 6 mo) stroke or transient ischemic attack	-CHADS-2 score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack, -Rheumatic valvular heart disease	-Recent (within 3 mo) VTE -Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, or multiple abnormalities)
<b>Medium</b>	Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age >75yr	- CHADS-2 score of 3 or 4	-VTE within the past 3 to 12 mo -Non-severe thrombophilic conditions (e.g., heterozygous factor V Leiden mutation, heterozygous factor II mutation) -Recurrent VTE -Active cancer (treated within 6 months or palliative)
<b>Low</b>	-Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	- CHADS-2 score of 0 to 2 (and no prior stroke or transient ischemic attack)	-Single VTE occurred > 12 mo ago and no other risk factors

From: The Perioperative Management of Antithrombotic Therapy; CHEST/133/6/June, 2008 Supplement; page 305S.

### **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 interruption or cause of the interruption. 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 (defined as INR below 1.8) for any duration of time.
3. Patients at moderate thrombotic risk require bridging when interruption of anticoagulation will be prolonged or for procedure that may be expected to significantly increase patients thrombotic risk, such as extensive surgery and/or anticipated post-operative immobilization or bedrest. Bridging should be with therapeutic-dose LMWH, although low dose LMWH may be acceptable under some circumstances. 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. Therefore, these patients require consideration on a case by case basis in consultation with a physician, either the anticoagulation management service chief or physician consultant, the PCP, or the appropriate specialist.
4. Patients at low thrombotic risk do not require bridging for interruption of anticoagulation for surgery, procedures, or other subtherapeutic occurrences. In some situations, post-operative immobilization may still require prophylactic dose LMWH after surgery.
5. Patients receiving bridging with therapeutic dose LMWH should receive their last dose of LMWH no closer than 24 hours before the procedure. They should receive only the morning dose if on a twice daily dosing schedule and only 50% of the total daily dose if on a once daily schedule.
6. Patients receiving prophylactic dose regimens who do not have reasons for low dosing such as renal failure may receive their full prophylactic dose up to 24 hours before the procedure.
7. Patients undergoing a minor surgical or other invasive procedure (low and some moderate risk procedures above) and receiving bridging before the procedure may resume the bridging regimen 24 hours after the procedure when there is adequate hemostasis.

### **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, assuming that 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.
  - Beginning low dose prophylactic LMWH once hemostasis is secured, and resuming therapeutic dose LMWH 48-72 hours after surgery.
5. The AMS manager will discontinue LMWH, if prescribed, once INR reaches therapeutic range.
6. Note: Anticoagulation managers will provide verbal and written instructions to all patients requiring a hold of warfarin for a procedure, and fax or electronically send a copy of the instructions to the physician performing the procedure.

### **Management of Patients Requiring LMWH:**

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

- Day (-5): Stop warfarin. (Note: in patients with INR > 3.0, warfarin may need to be held for 6-7 days prior to procedure.)
- Day (-3): Start LMWH (full or prophylactic dose depending on thromboembolic risk) in AM. LMWH is started 36 hours after stopping warfarin (assuming evening dose of warfarin and first dose of LMWH in AM).
- Day (-1): Discontinue LMWH 24+ hours prior to procedure. If twice daily schedule, take usual dose the morning of the day before surgery. If once daily dose and on treatment dose LMWH, reduce it by 50% and take the morning of the day before surgery. If on prophylactic daily dose, may take entire dose in morning of the day before surgery.
- Day (-1): Check INR (goal  $\leq 1.5$ ). If INR is > 1.5, Vitamin K 1mg (Aquamephyton solution taken orally) to 1.25mg (1/4 of 5mg pill) should be considered. If INR is 1.6 - 1.7 and is decreasing, Vitamin K is generally not needed; however, INR should be checked stat 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  $\leq 1.2$ ). If INR is > 1.2, Vitamin K 1mg (Aquamephyton solution taken orally) to 1.25mg (1/4 of 5mg pill) should be considered.
- Day (0): Procedure day.

#### ***Postoperative management:***

- Day (0) or Day (+1): Restart warfarin 12-24 hours after procedure, after hemostasis has been secured.
- **In all cases, timing of resumption of LMWH should be cleared by surgeon or other clinician (e.g. cardiologist implanting pacemaker or AICD) responsible for the procedure.** Options include deferring start of bridging LMWH for 48-72 hours at therapeutic dose or starting prophylactic dose LMWH on evening after surgery once hemostasis has been secured, then changing to therapeutic dose LMWH 48-72 hours after surgery. Spinal procedures are associated with high risk for post-operative bleed; no LMWH in any dose should be given for at least 24 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 9: ANTICOAGULATION MGT. FOR PATIENTS HAVING ORTHOPEDIC SURGERY

### Pre-Operative/6-INR-Operative Procedures for the Orthopedist:

1. The orthopedic surgeon or designee enters a referral for anticoagulation management either before or after hip arthroplasty (THR), hip fracture surgery (HFS), or knee arthroplasty (TKA). The referral must include the anticipated or actual date of surgery and a specific treatment plan in accordance with one the following options, which are considered equivalent in effectiveness for preventing venous thrombosis and safety in minimizing bleeding:

Procedure	Options for anticoagulation	Comments
<b>Elective THR and all hip fracture surgery (HFS)</b>	<b>Option 1:</b> LMWH started 12 hours before surgery or 12 hours after surgery at the full prophylactic dose	Anticoagulation should be continued for at least 10 days, and <u>recommended</u> for extension up to 35 days (5 weeks); duration is based on patient's thrombotic risk, as determined by the treating orthopedist. Although not in CHEST guidelines, it is reasonable to consider treating first with LMWH followed by dose-adjusted warfarin as noted.
	<b>Option 2:</b> LMWH started 4-6 hours after surgery at half usual prophylactic dose and then increased to full dose the following day.	
	<b>Option 3:</b> Fondaparinux 2.5 mg/day started 6-8 hours after surgery	
	<b>Option 4:</b> 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) <sup>36</sup>	
<b>Elective TKA, other knee and ankle procedures<sup>37</sup></b>	<b>Option 1:</b> LMWH started 12 hours before surgery or 12 hours after surgery at the full prophylactic dose	Anticoagulation should be continued for at least 10 days, and <u>suggested</u> for extension up to 35 days (5 weeks); duration is based on patient's thrombotic risk, as determined by the treating orthopedist. Although not in CHEST guidelines, it is reasonable to consider treating first with LMWH followed by dose-adjusted warfarin as noted. Elective knee arthroscopy does not require post procedure prophylaxis if early ambulation is possible and no other thromboembolic risk factors present.
	<b>Option 2:</b> Fondaparinux 2.5 mg/day started 6-8 hours after surgery	
	<b>Option 3:</b> 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) <sup>38</sup>	

<sup>36</sup> 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.

<sup>37</sup> Post-operative anticoagulation can be used after ankle surgery/fractures and other invasive knee procedures depending on co-morbidities.

<sup>38</sup> 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.

2. **If LMWH or Fondaparinux is used**, the orthopedic surgeon or designee is responsible for making arrangements for injection, teaching patient or family member or setting up home health services, and writing the prescription. Options include:
  - Lovenox 30mg SC bid
  - Lovenox 40mg SC qd (only if the patient requires visiting nurse or office visits for injections)
  - Fondaparinux 2.5 mg SC qd
3. 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.

### ***Hospital Discharge Procedures for the Orthopedist:***

1. The orthopedic surgeon or designee notifies the Anticoagulation Management Service **as early as possible but before 4pm** on the day the patient is discharged from the hospital. Preferred mode of notification is via Epic message to the local Anticoagulation Pool. Discharge notification must include:
  - Warfarin and/or Lovenox/Fondaparinux dosing in hospital.
  - INR results, if warfarin is being used.
  - Plan for dose on evening of discharge, since patient will generally be advised of this dose at time of discharge.
2. When notification is sent as outlined above, the Anticoagulation Management Service will assume responsibility for management on the day discharge.
3. 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.
4. 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 homedraws for patients discharged over the weekend).
5. The Anticoagulation Manager will manage anticoagulation therapy in accordance with the patient's treatment plan and Anticoagulation Management Service guidelines.

## Appendix 10: HYPERCOAGULABILITY EVALUATION (for reference only; to be done by PCP or referring clinician when indicated)

### Indications for Hypercoagulability workup<sup>39</sup>:

1. First VTE before age 45
2. Recurrent VTE
3. VTE with first degree relative with VTE
4. History of still birth fetus and contemplating another pregnancy
5. History of three or more unexplained spontaneous abortions and contemplating another pregnancy.
6. Spontaneous VTE in unusual location (upper extremity in absence of catheter or other trauma), mesenteric or cerebral vein).

Note: additional “softer” reasons for Hypercoagulability workup include:

1. **Consideration of stopping anticoagulation after acute treatment of DVT of undetermined cause. Presence of significant thrombophilia will affect decision to stop anticoagulation.** 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.
2. **Need for determination of use of LMWH for bridging in patients with DVT of undetermined cause receiving long-term anticoagulation beyond the initial acute period of 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.
3. **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. In the presence of known antibodies of this nature, 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.**

### Evaluation:

Test	Is test reliable while patient on warfarin?	Is test reliable while patient on heparin?	Comment
ANTI CARDIOLIPIN ANTIBODY IgG/IgM [86147D]	Yes	Yes	Can be done while patient on either warfarin or heparin.
BETA-2-GLYCOPROTEIN I	Yes	Yes	Can be done while patient on either warfarin or heparin.

<sup>39</sup> Bauer, KA. The Thrombophilias: Well-defined Risk Factors with Uncertain Therapeutic Implications. *Annals of Internal Medicine*. 1001;135(5):367-73.

<a href="#">ANTIBODY IgG/IgM [86146E]</a> <b>LUPUS ANTICOAGULANT (FUNCTIONAL ASSAY) [85613A]</b>	Yes, if INR <3.5	No, if on UFH Yes, if on LMWH and anti-factor Xa therapeutic	<ul style="list-style-type: none"> <li>Generally not necessary if Anti-Phospholipid Antibody is negative; if lupus anticoagulant suspected despite negative Anti-Phospholipid (e.g. appropriate clinical situation and aPTT elevated off heparin), should use functional assay such as dRVVT diluted Russell Venom Viper Test).</li> <li>When patient is on warfarin, patient's plasma must be diluted 1:2 with normal plasma before testing.</li> </ul>
<a href="#">ANTI PHOSPHOLIPID ANTIBODY (ELISA) [order as Miscellaneous Test]</a>	Yes	Yes	Can be done while patient on either warfarin or heparin.
<b>ANTITHROMBIN III TEST % [85301A]</b>	Yes	No	May be reduced by thrombosis, so should be done after clot has stabilized, off heparin.
FACTOR VIII ACTIVITY [85240]	No	No	May be increased by thrombosis, so should be done after clot has stabilized, off heparin.
HOMOCYSTEINE [83090A]	Yes	Yes	Can be done while patient on either warfarin or heparin. Should be done after an overnight fast on a normal diet.
<b>FACTOR V R506Q LEIDEN [83890H]</b>	Yes	Yes	Can be done while patient on either warfarin or heparin.
<b>PROTEIN C ACTIVITY [85303C]</b>	No (see comment)	Yes	May be decreased by warfarin; if normal while patient is on warfarin, there is no deficiency. Factor V Leiden mutation may give falsely low values.
<b>PROTEIN S ACTIVITY [85306C]</b>	No (see comment)	Yes	May be decreased by warfarin; if normal while patient is on warfarin, there is no deficiency. Factor V Leiden mutation may give falsely low values.
<b>PROTHROMBIN GENE (20210A) MUTATION [83891H]</b>	Yes	Yes	Can be done while patient on either warfarin or heparin.