Stamford Health
Anticoagulation Clinic

ANTICOAGULATION MANAGEMENT SERVICE PROTOCOL

Written by:
Isabelle Millet, PharmD, PhD, RPh
Anticoagulation Clinic Manager

Nicole DaSilva, PharmD, RPh
Anticoagulation Clinic Pharmacist

Date: 03/30/12

Revised Aug 2020
Reviewed and
Approved by P&T
Oct 7, 2020

Approved by: Dr Maher Madhoun, MD, MMM
Medical Director of Clinical Operations
Medical Director of the Anticoagulation Clinic, as of July 1 st 2021

PURPOSE: To outline the goals and standards of managing patients on anticoagulation therapy under a collaborative drug therapy management agreement

GOALS:

- The Outpatient Anticoagulation (AC) Clinic is designed to offer patients safe and effective management of oral anticoagulation therapy and to assist physicians in improving the quality of care provided to patients on anticoagulation therapy
- Our main goal is to improve patient's anticoagulation therapy outcomes, reduce complications of anticoagulation therapy and reduce hospitalization related to adverse drug events
- Specific goals to meet The Joint Commission's National Patient Safety Goals to "reduce the likelihood of patient harm associated with the use of anticoagulant therapy" include:
  a. Improve continuity of care for patients on anticoagulation therapy
  b. Maximize benefits of warfarin therapy by using approved protocols and evidence-based practice guidelines
  c. Reduce adverse effects associated with warfarin therapy and be able to reverse anticoagulation and address management of bleeding events by approved protocols and evidence based guidelines.
  d. Provide education to patients and their families and enhance patients understanding of their disease state and drug therapy
  e. Improve patient compliance to the prescribed drug regimen and educate on the importance of follow-up
  f. Educate patients on oral anticoagulants including warfarin, the new direct oral anticoagulants, and LMWH.

OBJECTIVES:

- Provide anticoagulation management service to patients who are either initiating or continuing oral anticoagulation therapy
- Offer a patient centered approach to monitor oral anticoagulation therapy, particularly warfarin
- Assist physicians in maximizing the benefits of warfarin therapy (alone or with LMWH as bridge therapy), by maintaining the patient's INR values within the optimal therapeutic range (see Appendix I).
- Assist physicians in the peri-operative managements of warfarin or direct oral anticoagulants
- Reduce adverse effects resulting from warfarin therapy by screening for drug-drug interactions, drug-disease state interactions, drug-food interactions and by assessing patients for symptoms of unusual bleeding or embolic events.
- Provide education and routine follow up for patients, including disease state or condition information, monitoring requirements, drug therapy consultations and drug compliance assessment.

I. CLINIC OPERATIONS/RESPONSIBILITIES

- The Anticoagulation Clinic is run by clinical pharmacists credentialed in Anticoagulation Therapy Management.
- Patients will be enrolled to the clinic only upon a referral from a primary care physician, cardiologist, or any other healthcare provider involved in the care of the patient.
- Once the patient is enrolled, the AC clinic assumes responsibility for the management of the patients' anticoagulation therapy by adhering to a protocol approved by the SH P&T committee.
- The clinic acts as the designee of the referring physician in managing anticoagulation of the referred patient.
- The clinical operational protocol utilized by the clinic will be reviewed and approved by the hematologists.
- The CoaguChek device calibration and standardization will be reviewed and approved by the head of the blood bank.

II. REFERRAL

- Patients will be scheduled for a visit at the AC Clinic only after referral from a physician is obtained. Patients may be referred to the AC Clinic at any stage of anticoagulation therapy.
- Referrals from hospitalists and/or residents for patients who have been discharged from the hospital will be accepted and patients managed during the interim under our medical director until an outpatient provider signs a referral for the patient.
- Physicians should complete and sign the "Anticoagulation Clinic Referral" form (see Appendix II) and Fax or electronically send it to the Clinic.
- A signed referral form will include:
    - Indication(s) for the anticoagulation therapy
    - Desired INR range
    - Current anticoagulation dosage (i.e. warfarin, enoxaparin)
    - Expected duration of therapy
    - Current medications list for reconciliation
    - Other medical conditions
    - Name and phone number of the primary care physician
- By signing the referral form the referring physician agrees to enter into a collaborative agreement with the ACC and acknowledges that the patient is managed according to a protocol approved by the P&T
    - Under Connecticut General Statutes sec 20-631(b) "A collaborative drug therapy management agreement may authorize a pharmacist to implement, modify or discontinue a drug therapy that has been prescribed for a patient, order associated laboratory tests and administer drugs, all in accordance with a patient-specific written protocol."

III. PATIENT REGISTRATION/PATIENT PROFILE

- Upon referral, all the patient information will be recorded by the pharmacist and captured using the Anticoagulation Management Software, CoagClinic™ from Acelis Connected Health
- A patient profile will be completed for each patient:
    - Age
    - Indication(s) for anticoagulation therapy
    - List of concomitant disease conditions (diabetes, recent MI, CHF, others)
    - List of current medications (prescriptions, OTC or herbal supplements)
    - Social history (married, single, alcohol consumption, etc..)
    - Dietary information (vitamin K rich food intake, etc..)
    - Name and current dose of anticoagulant
    - INR and warfarin dose history
    - Most recent blood test results (such as CBC, platelet, fecal blood test, urine analysis, others (if available)).

IV. INITIAL VISIT

- Upon referral, the staff from the clinic will schedule a patient for an initial visit.
    - If the patient is unable to be contacted within 2 weeks, then the referring provider will be notified that the patient was unable to be contacted and is, therefore, not currently being managed by the AC Clinic.
- Patients will be scheduled to meet with a pharmacist for an initial 30 minutes to review pertinent information and for assessing educational needs.
- The pharmacist will go over patient info to confirm identity, medical diagnoses and up-date the patient profile.
- The pharmacist will review patient's medications and diet profile for evaluation of drug and food interactions (see Appendix III, and Appendix IV). The pharmacist may request the patient to bring in all the medications he/she is taking at home for drug reconciliation.
- Patient will receive a warfarin brochure and other informative education materials on warfarin and food interactions as needed.
- The pharmacist will discuss with the patient the importance of keeping with their appointments and their INR monitoring in order to get the most benefit from their medication.
- Patient will be asked to review the Contract with the Patient letter between him and the ACC staff and to sign it the contract if they agree to the contract terms (see Appendix XVII). This contract will be valid throughout the enrollment of the patient with the ACC.

V. FOLLOW-UP VISIT PROTOCOL

- Follow up visits will be scheduled for a 15 minute session. Visits will be conducted as per protocol (as described below).
- The adherence to these follow-up visits is critical to ensuring adequate management of the patient's INR. The frequency of the follow-up visit for each patient will depend on the state of anticoagulation based on the INR profile.
- **Visit protocol:**
    - Patients are interviewed by the clinical pharmacist. During the visit, the clinical pharmacist will question the patient regarding (see Appendix V):
        - Recent illness
        - Current dosage or dose omission of warfarin
        - Significant changes in diet
        - Changes in concomitant drug therapy

        - GI illness (i.e. diarrhea, bloody stools, etc.)
        - Alcohol consumption
        - Symptoms of bleeding
        - Symptoms of a thrombotic event
    - The pharmacist will obtain vital signs: BP and pulse, will be taken by the pharmacist at each visit if the patient agrees. When BP is ≥180 and/or diastolic pressure ≥110, the patient's primary care physician and/or cardiologist will be contacted.
    - The pharmacist will evaluate the need for further complementary laboratory tests (CBC and platelets, urine analysis, occult fecal blood test, pregnancy test) and refer these patients to a Stamford Health laboratory draw station.
    - The pharmacist will evaluate patient compliance with anticoagulation therapy.
    - The pharmacist will update any new relevant information (telephone numbers, insurance, address, etc.).
    - The pharmacist will assess for educational needs.
- **End of the visit:**
    - At the end of the visit, the patient will be given dosage instructions and the next appointment date, determined by the pharmacist.
    - A patient summary with dosage instructions will be printed and given to the patient.

VI. PATIENTS WITH HOME DRAWN PT/INR

- When the patient is unable to come to the ACC, the ACC will make arrangements either with SH laboratory to get a PT/INR drawn at their house or for a pharmacist from the ACC to set up a visit including a PT/INR testing at the patient's house (see Home Based INR policy).
- Patients will be managed according to our current protocol.

VII. PT/INR MEASUREMENT (see Appendix VI, PT/INR POC testing, policy #100)

- The pharmacist will obtain a blood sample by finger stick and measure prothrombin time (PT)/International Normalized Ratio (INR) using a point of care testing system: CoaguCheck XS (Roche) (see PT/INR POC testing policy #100). The PT reagent used in this system contains human recombinant thromboplastin 1.5 U, as well as stabilizers and additives with an ISI=1.0.
- Correlation studies between in house laboratory reference test using venous blood and Coagucheck XS test using capillary blood showed a correlation index of 0.956 (n= 41). PT/INR results will be recorded in by the pharmacist using CoagClinic software and Meditech as well.
- Based on the patient assessment and PT/INR results, dosage changes will be made if necessary (when the value is outside of the desired therapeutic range) and the patient will be counseled on these changes.
- Note: When PT/INR observed value is markedly different from the expected value, another reading will be done and/or the patient will be referred to the blood drawing laboratory to get his blood drawn and his/her PT/INR retested.
- On going sampling control will be performed, and random POC PT/INR will be compared to venous blood PT/INR from SH laboratory to assess the quality of our testing
- **Limitations to this assay include:**
    - Limitations to accuracy and precision have been documented such as greater differences compared to standard venous based methodology as INR increases. Our in house correlation study indicates that POC INR and INR from SH laboratory correlates very well for INR up to 4.0.

- For INR value ≥ 4.0 with Coagucheck XS, another PT test using another batch of strip will be performed. The patient may be sent to the Tully blood lab to get his/her PT/INR retested by the lab, unless the patient refuses. In this case, another INR test will be done.
- For INR equal or above 6.0, the patient will be sent to the Tully testing Center or to any SH testing centers to repeat and confirm PT/INR.
- CoaguCheck system cannot be used in patients treated with direct thrombin inhibitors such as bivalirudin or argatroban.
- In patients with anti-phospholipids antibodies such as Lupus Anticoagulant (LA), a comparison to an APA-insensitive laboratory method is recommended (manufacturer statement). The same recommendation might apply for patients with factor V Leiden.
- Hematocrit above 55 % or below 25%: POC INR testing cannot be used. Patient needs to get INR tested by regular venipuncture.
- UFH concentrations up to 0.8 U/ml and LMWH up to 2 IU factor Xa activity /mL do not affect POC INR for INR values less than 2.9. INR values above 2.9 are influenced by the above UFH and LMWH.

VIII. PT/INR RESULTS EVALUATION/DOSAGE ADJUSTMENT

- **Initiation Dosing**
  - Initiation Dosing for "Sufficiently Healthy" Patients
    - The ACCP guidelines recommend the initiation of oral anticoagulation therapy with warfarin doses between 5 and 10 mg for the first 1-2 days for most individuals with subsequent dosing based on the INR response.
  - Initiation Dosing for Patients Who Might be Sensitive to Warfarin Therapy
    - Patients will be started on warfarin 2.5 mg for 2-3 days.
    - Increased sensitivity to warfarin therapy is observed in patients with:
      - Advanced age (>75 yrs)
      - Basal INR>1.3
      - Malnutrition
      - Congestive heart failure
      - Carcinoma
      - Thyroid conditions
      - Liver disease
      - CYP2C9 or VKORC1 genotypes
      - On medications that increase potency of warfarin such as amiodarone, Flagyl, Bactrim
  - A dosing nomogram for initiation of warfarin therapy may be used in particular in hospitalized patients (see Appendix IX).
  - For ambulatory patients and in particular patients with a goal INR: 2.0 -3.0, the following nomogram may be used.

Initiation of Warfarin Therapy in Naïve Patients

	Non-Sensitive Patients	**Sensitive Patients***
Initial Dose	5mg	2.5mg
First INR	3 days	3 days
< 1.5	5-7.5mg	2.5 5mg
1.5 - 1.9	2.5 -5mg	2.5mg
2-3	2.5mg	1.25mg
3.1-4	0- 1.25mg	0- 0.5mg

>4	Hold	hold
Next INR	2 - 3 days	2 - 3 days
Subsequent dosing and monitoring	Continue dose escalation and frequent monitoring until lower limit of therapeutic range is reached.	

Adapted from University of Washington Medical Center, Anticoagulation Services

- .**Maintenance Dosage Adjustment Based on Current INR Level:**
  - After reviewing the INR results and the patient's profile, the pharmacist will adjust the patient's anticoagulation therapy accordingly.
  - The dosing adjustment will be done using the empirical method (using the INR based nomogram shown below) and/or software suggestions, in addition to the pharmacist clinical judgment after interview with the patient and reviewing potential drug and/or food interactions (see Appendix III, Appendix IV).
  - Anticoagulation Empirical Dose Adjustment Protocol:

The following table indicates dose adjustment suggestions provided that discrepancies in the INR are not due to missed dose or other patient non-compliance issues.

Targeted INR 2.0-3.0		
INR	**Warfarin dose**	**Next INR**
<1.5	Increase weekly dose by 5-20 %	1 week
1.5-2.0*	Increase weekly dose by 10-15 %	1 - 2 week
2.0-3.0**	No dose change	4 -5 weeks***
3.1- 3.5	Decrease weekly dose by 5-15 %	1-2 week
3.6-4.0	Hold 1 dose then decrease by 10-15 %	4-8 days
>4.0	Repeat INR and if possible confirm with laboratory venous blood drawn. Hold for 1 or 2 days and decrease weekly dose by 15 %	2- 5 days
> 4.5	See Management of Warfarin Over anticoagulation table (see § IX.2)	

* If INR 1.8-1.9, consider no change and repeat INR within 1- 2 week
**If INR 3.1-3.2, consider no change and repeat INR within 1-2 week
*** For patients who have been in the INR range for over 6 -12 months, and with no issues (history of anemia, GI bleed or comorbidity), repeat INR could be at 5 weeks

Targeted INR 2.5-3.5		
INR	**Warfarin dose**	**Next INR**
<2.0	Increase weekly dose by 10-20%. Consider give extra dose on day of testing	4-8 days
2.0-2.5	Increase weekly dose by 5-15%	1 week
2.5-3.5	No dose change	4 - 5 weeks***
3.6- 4.0	Decrease by 10-15 %	1-2 week
4.1-4.5	Repeat INR and if possible confirm with laboratory venous blood drawn. Hold for 1 or 2 days and decrease weekly dose by 15 %	4-8 days

>4.5 <6.0	Repeat INR and if possible confirm with laboratory venous blood drawn. Hold 1 dose and decrease by 10-15 %	2- 5 days
> 4.5	See Management of Warfarin Over Anticoagulation table (see § IX.2)	

(Adapted from University of Michigan Cardiovascular Center
*If INR 2.3-2.4 consider no change and repeat INR in 1 week
*If INR 3.6-3.7 consider no change and repeat INR in 1 week
*** For patients who have been in the INR range for over 6 -12 months and with no issues (history of anemia, GI bleed or comorbidity), repeat INR could be at 5-6 weeks

Note: These are general guidelines. Adjustments may be made for individuals who may be more warfarin sensitive or those who are long- time stable patients.

- **Points to Consider in Addition to Dosing Nomogram:**
  - Always consider the trend in patient's INR when making warfarin management decision.
  - Consider repeating PT/INR the same day using venous blood if observed value markedly differs from expected value.
  - INR value will drop by 0.5 - 1.0 per day that warfarin is withheld.
  - Expect a 15 % dose adjustment to result in approximately 1.0 INR change. Likewise a 10 % dose adjustment will result in an approximately 0.7-0.8 INR change (ICSI Health care guideline: Antithrombotic Therapy Supplement, 2007).
- **Dosing Change Documentation**
  - Any change in dosing will be authorized by the pharmacist at the time of service and updated in the computerized file.
  - Patients will be instructed of these changes and given instruction regarding his/her new dosage.
  - Referring physicians will receive patient report and dosage info on the same day, via fax or electronically via Meditech or eCW.

- **Emergency Dosing of Warfarin Based on Current INR level:**
  - If a patient has run out or will run out of warfarin and is unable to obtain warfarin from their pharmacy within 24 hours, warfarin may be given in clinic as an emergency "bridge" supply (2-4 days).
  - If INR values are unstable with patient's current warfarin strength and regimen then a new warfarin strength may be administered in clinic as a trial before a new strength is prescribed.

IX. PT/INR MONITORING FREQUENCY

- The frequency of the monitoring of patient's INR will be based on the ACCP guidelines (9th edition).
- **Frequency of the Follow-Up Visit will be Dependent on:**
  - Initiation or Maintenance therapy
  - Patient's compliance
  - Fluctuations in co-morbid conditions
  - Changes in medications, diet
  - Stability of INR response
- **Patients Started on Warfarin Therapy:**
  - The ACCP guidelines suggest that INR monitoring should be started at the initial 2nd or 3rd dose of oral AC therapy. For patients started on warfarin as an outpatient, the INR

should be checked at first between days 3 to 5 of initiation. INR will be then tested either twice a week or weekly, depending on the INR and until INR is within desired therapeutic range. Once therapeutic, 2 consecutive weekly therapeutic INR, will be required before starting to extend monitoring frequency.

- **Patients With Stabilized INR:**
  - The ACCP guidelines (8th edition) suggest that the monitoring should be done at an interval no longer than every 4 weeks. The updated guideline (9th edition) allows re-testing up to 12 weeks.
  - At the clinic, for patients who have been therapeutic for over 6 -12 months and do not have any other issues such as history of anemia, GI bleed or CHF, we may allow repeat INR every 5-6 weeks.
  - When warfarin dose has been adjusted (within 10-15 % dosage change limit), visit will be scheduled within 1-2 weeks until INR goal has been achieved and stable (at least 2 consecutive INRs), or more frequently in presence of warfarin interacting issues (medications, illness, e.g. exacerbation of CHF, initiation of antibiotics, diarrhea….).
- **Patients With Unstable INR:**
  - INR in the medically unstable patients will be checked at least every 1-2 weeks.
  - In patients with significant over anticoagulation (≥5.0), INR will be checked within the next 3-5 days.

[1]Follow up Algorithm

# Consecutive "In- range" INRs	Frequency repeat INR
1	1 week
2	2 weeks
3	3 weeks
4	4 weeks
Note: If INR 2.0-2.1 or 2.9-3.0, consider repeat INR in 2 weeks regardless of # of consecutive in-range INRs	

X. MANAGEMENT OF ELEVATED INR

- **Management of Elevated INR Without Significant Bleeding**

When patient's INR value is ≥ 4.5 but < 6, and the patient presents non-significant risk factors for bleeding (see Appendix X), the pharmacist will adjust the dose of the patient according to the ACCP Guidelines (9th edition) by holding the dose for 1-2 days and recheck INR within 1-3 days. (see below:

	Recommendation
Management of Elevated INR Without Significant Bleeding	
INR 4.5 – 10 and no evidence of bleeding	Withhold warfarin and recheck INR within 24-48 hrs. Vitamin K administration is not recommended but may be considered for patients on antiplatelet agents.
INR > 10 and no evidence of bleeding	Withhold warfarin, give 1-5 mg oral vitamin K and recheck INR in 24 hrs; OR Withhold warfarin, administer 0.5-1 mg IV vitamin K and recheck INR in 24 hrs;
Bleeding or Urgent Surgery Required (with or without INR above therapeutic range)	

Serious or life-threatening bleeding at any elevation of INR or need for urgent surgery/invasive procedure (within 24 hrs)	Hold warfarin; give vitamin K 5-10 mg IV supplement 4F-PCC (Kcentra ®) or FFP when Kcentra is not available). Repeat treatment as necessary.
Major but non-life-threatening bleeding with any increase in INR	Hold warfarin; give vitamin K 5-10 mg IV and consider supplemental FFP as necessary

This has been updated upon the latest ACCP guidelines, 9th edition Warkentin et al., CHEST 2012; 141:7S-47S and 2017 ACC ECDP on Management of Bleeding in Patients on Oral Anticoagulants, JACC 2017; 70, 24

- **For INR ≥ 6.0 and/or any significant symptoms of bleeding and/or risk factors for bleeding (Appendix X), the referring physician and/or primary care physician will be contacted immediately**. Provided that oral dose of vitamin K is recommended by the referring physician, the pharmacist may call in an order for oral vitamin K or administer a dose of vitamin K PO, 2.5 mg or 5 mg in the clinic.

- **Management of Elevated INR With Signs of Bleeding**
  - In case of symptoms of bleeding with or without significant elevated INR, the referring physician will be notified immediately and the patient referred to the emergency room. See ACCP guidelines recommendations (Appendix XI).

XI. PERIOPERATIVE MANAGEMENT OF ANTICOAGULATION THERAPY

- Management of anticoagulation before and after invasive procedures requires patient-specific evaluation of the risk of bleeding associated with the surgical procedure as well as the risk of thromboembolism associated with the underlying disease state of the patient(see table below). Perioperative management plan for the patient will be made in consultation with the physician performing the procedure and/or the primary care physician, or the referring physician.

Assessing the Criteria To Initiate Bridging Anticoagulation			
	Indication for Warfarin Therapy		
Risk Stratum For Thromboembolic Events	**Mechanical Heart Valve**	**Atrial Fibrillation***	**VTE**
High	▪ Any mitral valve prosthesis ▪ Older (caged-ball or tilting disc) aortic valve prosthesis ▪ Recent (within 6 months) stroke or transient ischemic attack	▪ CHA_2DS_2-Vasc score >7, or $CHADS_2$ score of 5 to 6 ▪ Recent (within 3 months) stroke, transient ischemic attack, or any other thrombotic event ▪ Rheumatic valvular heart disease	▪ Recent (within 3 months) VTE ▪ Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, or multiple abnormalities)
Moderate	▪ Bileaflet aortic valve prosthesis and one of the following: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 years	▪ CHA_2DS_2-Vasc score 5 to 6, or $CHADS_2$ score of 3 or 4 ▪ History of embolic ischemic stroke, TIA or systemic embolism $\geq$ 3 months and < 1 year	▪ VTE within the past 3 – 12 months ▪ Non-severe thrombophilic conditions (e.g., heterozygous factor V Leiden mutation, heterozygous factor II mutation) ▪ Recent VTE ▪ Active cancer (treated within 6 months or palliative)
Low	▪ Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	▪ CHA_2DS_2-Vasc score 1-4, or $CHADS_2$ score of 0 to 2 and no prior hx of ischemic stroke, TIA or SE	▪ Single VTE occurred > 12 months ago and no other risk factors

The referring physician will be consulted regarding the perioperative management of the anticoagulation of their patient.

- **Perioperative Management of Patients With Atrial Fibrillation**:

The perioperative management of patients with atrial fibrillation will follow the recommendation from the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation (JACC 2017, vol 69: 871-898).

- For patients with CHA_2DS_2-Vasc score 1-4 and no prior TE, TIA or stroke, who have warfarin treatment interrupted for an elective operation or other elective invasive procedure, we suggest not to bridge anticoagulation.
- Patients with CHA_2DS_2-Vasc score 5-6 without Hx of a recent stroke or TIA, or patients who have a history of a thrombotic event > 3 months are considered at moderate risk for thrombotic events and may or may not be a candidate for bridging.
- Patients with a recent (within 3 months) thrombotic event, including stroke or TIA, or patients with CHA_2DS_2-Vasc score of $\geq$ 7, will be bridged with therapeutic dose of LMWH, or UFH in case of renal insufficiency.

- **Perioperative Management of Patients With Valve Replacement at Low risk of Thromboembolism (Appendix XIII)**
  Includes patients with prosthetic aortic valve (bileaflet or current-generation single tilting disk valve) WITHOUT atrial fibrillation or no other risk factors for thrombosis (i.e., hypercoagulable state, prior TE, or LV dysfunction
    - For patients undergoing minor procedures (such as cataract surgery, dental extraction or minor procedures), we will recommend to continue warfarin therapy, but to have INR checked 2-3 days prior the procedure.
    - For patients undergoing invasive or surgical procedures, we will suggest temporary interruption of warfarin for 3-5 days without bridging. Patients will be asked to get their INR tested 5 to 6 days prior to the surgery.
    - In patients whose INR is still elevated (≥1.5) one day before surgery, the pharmacist will call the physician to discuss administration of vitamin K (PO 1- 5 mg) or IV 10 mg) or to postpone surgery.
    - Warfarin will be resumed approximately 12 -24 h after surgery and when there is adequate hemostasis. The pharmacist will recommend using a "boost" dose (1.5 to 2x the regular dose) on the first day of resuming warfarin and INR check within the next 3 days.

- **Perioperative Management of Patients With Valve Replacement at Moderate to High Risk of Thromboembolism (Appendix XIII)**

  Includes patients with any mitral valve prosthesis, older generation prosthetic aortic valve (any caged ball valve) or current generation of mechanical aortic valve (bileaflet or single tilting disk) WITH a recent stroke or TIA, or WITH atrial fibrillation or CHF with LVEF<30 %, or history of thromboembolism, or hypercoagulable condition.

    - In patients undergoing invasive procedures, warfarin will be stopped 3 to 6 days before surgery depending on the bleeding risk of the surgery. Patient will be bridged with LMWH. When INR falls to 2.0 or less, initiation of LMWH will be recommended. The pharmacist will recommend therapeutic dose of LMWH, enoxaparin 1 mg/kg q12h or 1.5 mg/kg q24h or 1 mg/kg q24h (for creatinine clearance ≤ 30 ml/min). For patients with severe CKD, UFH might be preferred.

        - Before Surgery:
            - The last dose of Enoxaparin should be given 24 hours before surgery or procedure. The last pre-operative dose of LMWH administered should be 50% of the total daily dose instead of the full dose.

        - After Surgery:
            - Resume therapeutic dose of Enoxaparin 12-24 h after surgery/procedure, when there is adequate hemostasis.
            - In patients undergoing major surgery or with high risk of bleeding, the recommendation is to delay the initiation of Enoxaparin for 48 to 72 h after surgery.
            - Warfarin should be resumed within 24 h of the surgery.

    - Enoxaparin injections may be administered in at the Anticoagulation/MTM Clinic if the patient is unable to inject themselves or a caregiver is unable to administer it.

- **Perioperative Management of Patients With Previous VTE at Low risk of Thromboembolism**

Includes patients without risk factors who had the previous VTE > 12 months ago

  - In patients with low risk of thromboembolism undergoing invasive procedures, no bridging therapy will be recommended. The pharmacist, according to the ACCP guidelines will recommend the patient to stop warfarin 3-5 days before surgery and resume it within 24 h of the procedure.

- **Perioperative Management of Patients With Previous VTE at Moderate to High Risk of Thromboembolism**

Includes patients with a recent VTE and thrombotic conditions (detailed criteria identified in the table above)
Our recommendations (see table below) will be based on the current practice (American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy, Blood Adv. 2018 Nov 27;2(22):3257-3291).

Thromboembolism Risk	Recommendation for Managing Anticoagulation Therapy
High risk of thromboembolism	Discontinue warfarin 5 days before surgery. Provide bridging anticoagulation with therapeutic-dose SQ LMWH (Lovenox®: 1mg/kg q12h or 1.5 mg/kg q24h or 1mg/kg q24 h when creatinine clearance ≤30 ml/min).
Moderate risk of thromboembolism	Discontinue warfarin 3-5 days before surgery. Bridging or not bridging the patient will be based on patient specific factors Prophylactic dose of LMWH(40 mg daily) may be preferred over therapeutic dose except in case of higher risk of thrombosis procedure. In higher risk patients provide bridging anticoagulation with therapeutic-dose SQ LMWH (Lovenox®: 1mg/kg q12h or 1.5 mg/kg q24h or 1mg/kg q24 h when creatinine clearance ≤30 ml/min)
Monitoring: Routine monitoring of anti-factor Xa levels is not recommended in patients receiving bridging anticoagulation with LMWH. However, platelets count should be monitored every 2 or 3 days from day 4 to day 14.	

- **Perioperative Management of Patients Requiring Dental Procedures/or Cataract Surgery**

  - Management of anticoagulation before and after dental procedures requires careful patient-specific evaluation of the risk of bleeding associated with the dental procedure as well as the risk of thromboembolism associated with the underlying disease state for which anticoagulation is indicated.
    Patient specific management plans will be made in consultation with the dentist performing the procedure (see Appendix XIV).

  - For cataract surgery, unless requested by the ophthalmologist, in agreement with the referring physician, holding warfarin will not be recommended.

- **VTE Prophylaxis: Bridging LMWH to Warfarin Therapy**

- For orthopedic patients, the pharmacist upon referral can help manage warfarin bridging therapy for patients who underwent orthopedic surgery (elective hip or knee surgery). (See Appendix XV).

XI. EVALUATION OF POTENTIAL DRUG-DRUG AND DRUG FOOD INTERACTIONS (See Appendix III, and Appendix IV)

- After reviewing the patient's list of medications and diet, the clinical pharmacist will evaluate drug and food interactions, before adjusting the patient's warfarin dose.
- The Anticoagulation Management software CoagClinic™ allows the tracking of patient's medications and provides a built-in list of over 2,000 medications with pop-up information alerting the pharmacist about potential drug interactions with warfarin.

XII. REQUIRED CONSULTATION WITH THE REFERRING OR ATTENDING PHYSICIAN

- In the situations presented below, the referring physician, and/or the primary care physician or the Anticoagulation/MTM Clinic medical director will be notified immediately:
  - SBP ≥180 or DBP ≥110
  - INR within range but signs of thrombosis or bleeding
  - INR ≥6.0
- In most instances discontinuing warfarin therapy is determined by the referring provider; however, if a patient's warfarin therapy is discontinued (eg. from an outside provider or hospital) and the referring provider is not made aware, the pharmacist will notify the referring physician within 24 hours of the discontinuation.
- The referring physician will also be consulted if the patient is deemed a candidate for a direct oral anticoagulant (DOAC) after evaluation by the pharmacist. The pharmacist and physician will determine together if a patient is to discontinue warfarin in favor of another anticoagulant.

XIII. MANAGING NON-ADHERENCE AND ABSENCE FROM THE ACC

- **Patients who require frequent monitoring** (recent initiation of warfarin therapy or Hx of unstable INRs or medications requiring closer monitoring): after 2 weeks of due-date, and inability to reschedule the patient, the ACC will contact the referring physician to seek active practice support.
- **Patients who are in stable management**: After a patient's no-show appointment, the patient will be contacted via phone call or letter to reschedule appointment. After 6-12 weeks of no-shows and impossibility of rescheduling the patient, the ACC will contact and inform the referring physician.
- **Disenrollment of the patient:**
  - Patients will be disenrolled from the clinic at the time of the expiration of their referral (3, 6 or 12 months).-
  - For patients on long term anticoagulation therapy, after 12 months of no show, the patient or the referring physician will be informed of his/her disenrollment from the ACC.

XIV. OTHER RESPONSIBILITY OF THE PHARMACIST

- The clinical pharmacist may phone in a warfarin or LMWH prescription refill to the pharmacy of the patient's choice when needed.
- The pharmacist can also call in an oral vitamin K prescription or administer vitamin K in clinic upon the physician's agreement.

- The pharmacist can provide LMWH injection to the patient when needed.

XV. FOLLOW-UP WITH THE REFERRING PHYSICIAN AND PRIMARY CARE PHYSICIAN

- Any changes to the dosing regimen or issues regarding patient‘s conditions will be noted by the pharmacist and tracked in the CoagClinic™ software. The printed report may be faxed to the referring physician and/or primary care physician by request.
- At each visit, PT/INR values will be recorded in Meditech and information regarding warfarin dose regimen is also recorded. These reports will be available for the referring physician at least every 4 to 6 weeks (depending on the stability of patient’s INR and their frequency of requiring INR follow-up). If a patient is absent from the clinic, a report will not be generated, but the referring physician will be contacted (see section XIII).

XVI. PATIENT EDUCATION

- Education is one of the most important components of a successful anticoagulation management program and a main component of the NPSG 3E.
- Verbal, written, and occasionally audio-visual materials will be given to the patient.
- The patient will also be evaluated for his/her knowledge of the following during the course of therapy:
  - Name, strength, dose, description of the medication
  - Indication of the medication
  - How the drug works
  - Understanding the disease state
  - Administration (time and method)
  - Importance of keeping medication away from children
  - Potential drug-drug interactions
  - Potential drug-food interactions
  - Symptoms of unusual bleeding or bruising
  - Symptoms of thrombotic events
  - Procedures to follow for dental interventions
  - Procedures to follow in case of surgical procedures
  - Importance of compliance with treatment regimen

XVII. DOCUMENTATION

- Patient profiles will be updated at each visit: changes in medications, in diet, in anticoagulation dose, personal situations, contact number, etc.).
- Pharmacist will maintain a complete file on patients using CoagClinic software and also keep a printed record of the patient’s visit progress notes for the next visit.
- Pharmacist will record the INR result into Meditech.

XVIII. CONTINUOUS QUALITY IMPROVEMENT

- The Anticoagulation/MTM Clinic manager will prepare a quarterly and annual report to be reviewed by the Clinic’s medical director and the P&T Committee.
- This report will consist of:
  - Number of clinic visits and INRs performed
  - Number and percent of INR within therapeutic range
  - Time in therapeutic range (INR +/- 0.2)
- If needed, the AC clinic coordinator can provide other quality and safety data such as:

  - Number and percent of INRs above and below target range
  - Number and type of bleeding or thrombotic complications, treatment failures and other adverse events, emergency departments visits can be given when needed
- CoaguCheck XS quality controls (e.g. split sampling: comparison PT/INR results obtained with Coagucheck XS and the SH laboratory test).

XIX. DISCHARGE

- A patient will be discharged from the Clinic for any of the following circumstances:
  - The course of the therapy is complete
  - The patient refuses further treatment
  - Chronic non-compliance with management protocols
  - Repeated missed appointments (after 6-12 months)

XX. BILLING

- A charge will be generated through Meditech Lab. The following codes will be utilized:
  - PT test: CPT code 85610 QW
  - New patient visit: CPT code 99211
  - Follow up visit: CPT code 99211

XXI. References

1. Ansell J.E., Oertel L.B., and Witkowsky A.K. Clinical and Operational Guidelines; 2001
2. Antithrombotic and Thrombolytic Therapy, 9th Ed: ACCP Guidelines: CHEST / 141 / 2 / February, 2012 supplement
3. Garwood CL, Dumo P, Baringhaus SN, Laban KM. Pharmacotherapy. 2008; 28:20-6
4. Y. Zhu, M. Shennan, K.K. Reynolds, N. A. Johnson, M. R. Herrnberger, R. Valdes Jr, and M.W. Linder. Clin. Chem., 2007, 53: 1199-1205
5. UI Schwarz, MD Ritchie, Y. Bradford, C. Li, S.M. Dudek, A. Frye-Anderson, R.B. Kim, D.M. Roden, and M. Stein. N. Engl. J. Med., 2008:, 358: 999
6. HS Schelleman, J. Chen, Z. Chen, J. Christie, C.W. Newcomb, C.M. Brensinger, M. Price, A.S. Whitehead, C. Kealey, C.F. Thorn, F.F.Samaha, and S.E. Kimmel. Clin. Pharmacol. Ther., 2008, 84: 332
7. GH Guyatt, et al. . Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians: Evidence-Based Clinical Practice Guidelines. Chest, 2012:141 (2) Suppl: 7S-41S
8. AHA/ACC Guideline for the Management of Patients With ValvularHeart Disease, Executive Summary**,** Journal of the American College of Cardiology, 2014, 129:23

9-

9. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. Circulation. 2017;135:e1159–e1195.

Appendices

Appendix I: Target INR
Appendix II: Referral form
Appendix III: Drug-Drug Interactions
Appendix IV: Drug-Food, Drug-Herbal interactions
Appendix V: Patient Assessment Questionnaire
Appendix VI: PT/INR Measurement using Coagucheck XS Protocol
Appendix VII: Warfarin Sensitivity Factors
Appendix VIII: Warfarin dosing algorithms
Appendix IX: Dosing nomogram for initiation of warfarin
Appendix X: Risk factors for bleeding
Appendix XI: Management of elevated INR associated with bleeding
Appendix XII: Stratification of risk factors for thromboembolism
Appendix III: Anticoagulation management In Prosthetic Heart Valves
Appendix XIV: Perioperative management before and after dental procedures
Appendix XV: VTE prophylaxis: LMWH to Warfarin Bridging Therapy
Appendix XVI: Anticoagulation management software: CoagClinic™

Appendix I: Target INR

INDICATION	TARGET INR (RANGE)	DURATION
ATRIAL FIBRILLATION (AF)/ATRIAL FLUTTER		
Age ≤ 75 with no risk factors	*none*	chronic
With 1 risk factors	2.5 (2.0 - 3.0)	chronic
With 2 or more risk factors	2.5 (2.0 - 3.0)	chronic
[risk factors: age > 75; hx HTN; diabetes; CHF or moderate/severe LV dysfxn]		
With mitral stenosis or prosthetic heart valve	2.5 (2.0 – 3.0)	chronic
With prior history of stroke/TIA/systemic embolism	2.5 (2.0 – 3.0)	chronic
Following open heart surgery (in NSR)	2.5 (2.0 – 3.0)	4 weeks
pre-cardioversion (Afib or flutter > 48 hours)	2.5 (2.0 - 3.0)	3 weeks
post-cardioversion (in NSR)	2.5 (2.0 - 3.0)	4 weeks
ISCHEMIC STROKE		
Non-cardioembolic stroke or TIA	none	chronic
Cardioembolic stroke or TIA	2.5 (2.0 – 3.0)	chronic
~ with contraindications to warfarin	none	chronic
~ associated with aortic atherosclerotic lesions	none	chronic
~ associated with mobile aortic arch thrombi	2.5 (2.0 – 3.0)	chronic
~ associated with patent foramen ovale	none	chronic
MYOCARDIAL INFARCTION (MI)		
following MI	2.5 (2.0 - 3.0)	up to 4 years
following MI in high risk patients	2.5 (2.0 - 3.0)	at least 3 months
[anterior MI, significant heart failure, intracardiac thrombus, hx TE]		
THROMBOEMBOLISM (DVT, PE)		
treatment/prevention of recurrence **(including calf vein DVT, UE DVT, UE DVT associated with catheter**		
• transient risk factors	2.5 (2.0 - 3.0)	3 months
• unprovoked/first event		
~ proximal DVT or PE	2.5 (2.0 - 3.0)	chronic
~ distal DVT	2.5 (2.0 - 3.0)	3 months
• unprovoked/second event	2.5 (2.0 - 3.0)	chronic
• with malignancy	2.5 (2.0 – 3.0)	chronic
chronic thromboembolic pulmonary hypertension	2.5 (2.0 – 3.0)	chronic
cerebral venous sinus thrombosis	2.5 (2.0 – 3.0)	up to 12 months
spontaneous superficial vein thrombosis	2.5 (2.0 – 3.0)	4 weeks
VALVULAR DISEASE		
mitral valve prolapse		
• with TIAs or ischemic stroke	none	chronic
• with recurrent TIA despite ASA therapy	2.5 (2.0 - 3.0)	chronic
Mitral annular calcification with AF	2.5 (2.0 - 3.0)	chronic
rheumatic mitral valve disease:		
• with AF, hx systemic emb, LA thrombus, LA>55mm	2.5 (2.0 - 3.0)	chronic
• s/p thromboembolic event despite anticoagulation	2.5 (2.0-3.0)	chronic
VALVE REPLACEMENT – BIOPROSTHETIC		
aortic	none	chronic
mitral	2.5 (2.0 – 3.0)	3 months
with LA thrombus	2.5 [2.0 - 3.0]	until resolution
with prior history systemic embolism	2.5 [2.0 - 3.0]	at least 3 months
with additional risk factors for thromboembolism	2.5 [2.0 - 3.0]	chronic
[AF, hypercoagulable condition, low EF]		
VALVE REPLACEMENT - MECHANICAL		
aortic • bileaflet in NSR w/ nl LA size	2.5 (2.0 – 3.0)	chronic
• Medronic Hall tilting disk in NSR w/ nl LA size	2.5 (2.0 - 3.0)	chronic
• following prosthetic valve thrombosis	3.5 (3.0 – 4.0)	chronic
mitral • bileaflet or tilting disk	3.0 (2.5 - 3.5)	chronic
• following prosthetic valve thrombosis	4.0 (3.5 – 4.5)	chronic
caged ball or caged disk (aortic or mitral)	3.0 (2.5 – 3.5)	chronic
with additional risk factors for thromboembolism	3.0 (2.5 – 3.5)	chronic
[AF, MI, LA enlargement, hypercoagulable condition, low EF]		
with systemic embolism despite adequate anticoagulation	increase INR goal	chronic

Optimal Therapeutic Range and Duration of Anticoagulation
(from Antithrombotic and Thrombolytic Therapy: ACCP Evidence Based Clinical Practice Guidelines, 8th ed, 2008)

Appendix II: Referral Form

Appendix III: Drug-Drug Interactions

Drug interactions with warfarin are numerous and may cause an increase or decrease of warfarin blood level leading to possible harmful complications.
List of a selected list of most common Warfarin-Drug Interactions (from Warfarin Therapy: Evolving Strategies in Anticoagulation http://www.aafp.org/afp/AFPprinter/990201)

	Characteristics of interaction				
Drug	**Severity**	**Onset**	**Evidence**	**Mechanism**	**Management of interaction**
Acetaminophen (Tylenol)	Minor	Delayed	Poor	• Inhibits warfarin metabolism	• Advise patient to limit total acetaminophen dosage to less than 2 g per day; if higher dosages are used, increased monitoring may be necessary.
Allopurinol (Zyloprim)	Moderate	Delayed	Poor	• Unknown	• Monitor INR when allopurinol is added or withdrawn.
Amiodarone (Cordarone)	Moderate	Delayed	Excellent	• Decreases warfarin metabolism within a week of coadministration; effect may persist for 1 to 3 months after discontinuation of amiodarone • May induce hypothyroidism or hyperthyroidism	• A 25 percent reduction in the warfarin dosage is recommended when amiodarone is initiated. • Monitor INR closely when amiodarone is added or withdrawn.
Antifungal agents	Major	Delayed	Good	• Fluconazole (Diflucan), ketoconazole (Nizoral) and miconazole (Monistat) decrease warfarin metabolism	• Monitor INR when azole antifungals are added or withdrawn.
Antithyroid drugs	Moderate	Delayed	Fair	• Hyperthyroidism results in metabolism of vitamin K clotting factors and increased sensitivity to oral anticoagulants	• Monitor INR when antithyroid medications are added or withdrawn.
Barbiturates	Major	Delayed	Excellent	• Increase warfarin metabolism and frequently reduce	• Monitor INR when barbiturates are added or withdrawn; the addition of

				hypoprothrombinemic effect of warfarin	warfarin in patients stabilized on a chronic barbiturate regimen is of less significance.
Binding resins	Moderate	Delayed	Good	• Decrease absorption and may interrupt enterohepatic recirculation of warfarin	• Use colestipol (Colestid), which has a lower potential for interaction, instead of cholestyramine (Questran) in patients who need a bile sequestrant.
Carbamazepine (Tegretol)	Moderate	Delayed	Fair	• Increases warfarin metabolism	• Monitor INR intensively when carbamazepine is added or discontinued. • Increase warfarin doses when carbamazepine is added, and reduce doses when carbamazepine is discontinued (stabilization occurs after 4 to 6 weeks).
Cephalosporins	Moderate	Delayed	Poor	• Methylthiotetrazole ring in cefoperazone (Cefobid), cefamandole (Mandol), cefotetan (Cefotan) and cefmetazole (Zefazone) inhibits production of vitamin Kdependent clotting factors	• Avoid concomitant use of warfarin and cefoperazone, cefamandole, cefotetan or cefmetazole.
Cimetidine (Tagamet)	Moderate	Delayed	Excellent	• Inhibits warfarin metabolism; predominantly affects R isomer	• Use alternative agents in patients receiving warfarin. • Monitor INR when concomitant use of warfarin and cimetidine is necessary.
Contraceptives, oral	Minor	Delayed	Poor	• May increase clotting factor synthesis • May inhibit oxidative metabolism	• If possible, avoid oral contraceptives because of increased risk of thromboembolism • Monitor INR frequently when oral contraceptives are used concurrently with warfarin.
Corticosteroids	Moderate	Delayed	Poor	• Produce hypercoagulability • May have ulcerogenic effects	• Monitor for gastric toxicity.
Danazol (Danocrine)	Major	Delayed	Good	• May increase endogenous anticoagulants	• Monitor prothrombin time and INR for 2 days to 3 weeks after danazol is added.

Diflunisal (Dolobid)	Moderate	Delayed	Fair	• Displaces warfarin from protein binding, inhibits platelet aggregation, causes gastric erosions	• If possible, avoid concomitant use of warfarin and diflunisal. • Monitor INR if concomitant use is necessary.
Disulfiram (Antabuse)	Moderate	Delayed	Fair	• Inhibits warfarin metabolism	• If possible, avoid concomitant use of warfarin and disulfiram. • Monitor INR if concomitant use is necessary.
Ethanol	Moderate	Delayed	Excellent	• Acute ethanol use may inhibit anticoagulant metabolism. • Chronic ethanol use induces liver enzymes. • Cirrhosis is associated with reduced warfarin metabolism.	• Caution patients to drink in moderation and to avoid binge drinking. • Because liver damage results in greater sensitivity to warfarin, use lower starting doses.
Fluvoxamine (Luvox)	Moderate	Delayed	Fair	• Probably inhibits warfarin metabolism	• Monitor INR more closely for 1 to 2 weeks after fluvoxamine is started.
Heparin	Moderate	Rapid	Good	• Has additive anticoagulant effects	• Heparin may prolong INR, and warfarin may prolong partial thrombin time. • Be aware of small risk of bleeding events.
HMG CoA reductase inhibitors	Moderate	Delayed	Poor	• May inhibit warfarin metabolism	• Note that lovastatin (Mevacor) is more commonly associated with hypoprothrombinemia.
Isoniazid (Laniazid)	Moderate	Delayed	Poor	• May inhibit warfarin metabolism	• Monitor INR when isoniazid is added or withdrawn.
Metronidazole (Flagyl)	Moderate	Delayed	Fair	• Inhibits metabolism of S enantiomer of warfarin	• Avoid concomitant use of warfarin and metronidazole. • Monitor INR if concomitant use is necessary.
Nalidixic acid (NegGram)	Moderate	Delayed	Poor	• Displaces warfarin from protein-binding sites • Inhibits warfarin metabolism	• Avoid concomitant administration of warfarin and nalidixic acid. • Monitor INR if concomitant use is necessary.
NSAIDs	Moderate	Delayed	Fair	• Inhibit platelet aggregation	• Advise patients to avoid NSAIDs or to use them only

				• Cause gastric erosions	intermittently. • Instruct patients to take NSAIDs with food or antacids. • Consider having patients take misoprostol (Cytotec) to reduce risk of gastric erosions.
Paroxetine (Paxil)	Moderate	Delayed	Poor	• Probably inhibits warfarin metabolism	• Monitor INR frequently when paroxetine is added.
Penicillins	Moderate	Delayed	Fair	• Dicloxacillin (Pathocil) and nafcillin (Unipen) may enhance warfarin metabolism. • Penicillin may reduce gastrointestinal flora synthesis of vitamin K.	• Monitor INR: dicloxacillin and nafcillin decrease INR, and penicillin increases INR.
Phenytoin (Dilantin)	Major	Delayed	Fair	• Induces warfarin metabolism • Displaces warfarin from protein-binding sites • Enhances metabolism of clotting factors	• Monitor INR frequently for 1 month or more after phenytoin is added.
Propafenone (Rythmol)	Moderate	Delayed	Fair	• Probably inhibits warfarin metabolism	• Monitor INR frequently when propafenone is added or discontinued.
Quinolones	Moderate	Delayed	Poor	• Possibly inhibit warfarin metabolism	• Monitor INR.
Rifampin (Rifadin) and rifabutin (Mycobutin)	Moderate	Delayed	Poor	• Induce hepatic enzymes • Increase warfarin metabolism	• Monitor INR closely for 1 to 2 weeks after rifampin or rifabutin is added.
Salicylates	Major	Delayed	Excellent	• Inhibit platelet aggregation • Cause gastric erosions • In large doses, result in hypoprothrombinemic effect	• If possible, avoid concurrent use of warfarin and salicylates. • If aspirin is needed, advise patients to use a small dosage (325 mg or less per day). • Consider having patients take misoprostol to reduce the risk of NSAID-induced ulceration.
Sulfinpyrazone (Anturane)	Moderate	Delayed	Excellent	• Inhibits warfarin metabolism	• If possible, avoid concomitant use of warfarin and sulfinpyrazone. • Monitor for bleeding when concomitant use is necessary.

Thyroid hormones	Moderate	Delayed	Excellent	• Increases catabolism of vitamin Kdependent clotting factors	• Monitor INR frequently for 1 to 2 months.
Ticlopidine (Ticlid)	Moderate	Delayed	Poor	• Inhibits R enantiomer of warfarin • Inhibits platelet aggregation	• Monitor for bleeding.
Trimethoprim-sulfamethoxazole (Bactrim)	Major	Delayed	Excellent	• Sulfonamide component may stereoselectively inhibit S isomer metabolism.	• If possible, avoid concurrent use of warfarin and trimethoprim-sulfamethoxazole. • Monitor INR when concomitant use is necessary.
Vitamin E	Moderate	Delayed	Fair	• May interfere with production of clotting factors	• Interaction is probably dose-related and more likely to occur with vitamin E dosages greater than 800 U per day; monitor INR if larger dosages are taken.
Vitamin K	Moderate	Delayed	Excellent	• Effects of oral anticoagulants are directly antagonized by the excessive ingestion of foods or dietary supplements containing vitamin K.	• Advise patients to eat a consistent diet and to avoid taking large doses of vitamin supplements containing a great deal of vitamin K.

INR=International normalized ratio; HMG-CoA=3-hydroxy-3-methylglutaryl coenzyme A; NSAIDs=nonsteroidal anti-inflammatory drugs. Adapted with permission from Havrda DE, Anderson JR, Talbert RL. Thrombosis. In: Pharmacotherapy self assessment program module 1 cardiovascular. Kansas City, Mo.: American College of Clinical Pharmacy, 1998. Retrieved September 1998 from the World Wide Web at http:www.accp.com/psap3-des.html. Additional information derived from Warfarin. In: Drugdex. Englewood, Colo.: Micromedex Inc., 1998.

Appendix IV: Drug-Food, Drug-Herbal Interactions

Interactions of warfarin with food with herbal medicines are listed in the Warfarin/Coumadin® package insert. Additional information derived from Warfarin can be found in: Drugdex. Englewood, Colo.: Micromedex Inc., 1998.

Appendix V: Patient Assessment Questionnaire

Since your last visit at the clinic;

Have you experienced any lifestyle changes? Y____, N____

If yes, explain _____

Have you noticed increased bleeding or bleeding?

Gum bleeding while brushing teeth	Y____, N____
Occasional nosebleed	Y____, N____
Easy bruising	Y____, N____
Prolonged bleeding after minor cuts	Y____, N____
Prolonged menstrual bleeding	Y____, N____
Red, dark, coffee or cola colored urine	Y____, N____
Coughing red sputum	Y____, N____
Severe unprovoked pain (abdominal, severe headache)	Y____, N____

Have you noticed any signs of clotting:

Sudden weakness in any limb	Y____, N____
Numbness or tingling anywhere	Y____, N____
Visual changes or loss of sight in either eye	Y____, N____
Dizziness or faintness	Y____, N____
New pain, swelling, redness or heat in any extremity	Y____, N____
New shortness of breath onset	Y____, N____

Have you changed your diet in any way? Y____, N____

If yes, please explain_____

Have you started a new medication, vitamins, herbal supplements? Y____, N____

If yes, please explain_____

Have you changed anything else in your daily routine? Y____, N____

If yes, please explain

Have you been scheduled for a surgical, invasive, or dental procedure? Y____, N____

If yes, explain

Are you pregnant, or planning to get pregnant? Y____, N____

Have you omitted to take your dose of warfarin? Y____, N____

If yes, explain

Have your changed your schedule in taking your warfarin? Y____, N____

Do you have any questions about your warfarin therapy? Y____, N____

If yes, explain

Appendix VI: PT/INR Measurement using Coagucheck XS Protocol

See separate document**.**

Appendix VII: Warfarin Sensitivity Factors

Response to warfarin is highly variable both inter-individually and inter-ethnically. It is influenced by various factors. The most prevalent are.

- Age
- Body weight or BSA
- Drug Interactions
- Diet
- Disease state; CHF, malnutrition, liver disease
- Genetic: CYP2C9 alleles: alleles *1, *2 or *3

VKORC1 SNPs.

Appendix VIII: Warfarin Dosing Algorithms

1- CoagClinic™ Software Dose Adjustment Algorithm

The CoagClinic™ software offers the possibility to use the dosing algorithm described in the British Medical Journal: PJ Ryan, M Gilbert, PE Rose, Computer control of anticoagulant dose for therapeutic management. 1989, 299: 1208. See below:

The recommended dose is calculated as follows.

If the international normalised ratio >120% of target (mean of therapeutic range):

$$\text{Dose} = \left(\sqrt[3]{\frac{\text{target} + 20\%}{\text{today's international normalised ratio}}} \right) \times \text{previous dose}$$

If the international normalised ratio <80% of target (mean of therapeutic range):

$$\text{Dose} = \left(\sqrt[3]{\frac{\text{target} - 20\%}{\text{today's international normalised ratio}}} \right) \times \text{previous dose}$$

Appendix IX: Dosing Nomogram for Initiation and maintenance of Warfarin therapy

Initiation Anticoagulation Therapy Nomogram: Goal INR Range of 2-3

Target INR Goal of 2 -3		
Day	Warfarin Starting Dose (mg)	INR Value
Day 1	5 mg	< 1.3
Day 2	5 mg	< 1.5
	2.5mg	1.5 – 1.9
	0- 1.25 mg	2 – 2.5
	0 mg	> 2.5
Day 3	5 – 10 mg	< 1.5
	2.5 – 5 mg	1.5 – 1.9
	0 – 2.5 mg	2 – 3
	0 mg	> 3
Day 4	7.5- 10 mg	< 1.5
	5 – 7.5 mg	1.5 – 1.9
	2.5– 5 mg or continue last dose	2 2.5
	1.25- 2.5 mg	2.6 - 3
	0 mg	> 3
Day 5	10 mg	< 1.5
	7.5 – 10 mg	1.5 – 1.9
	2.5-5 mg or continue last dose	2 – 2.5
	2.5 - 5 mg	2.6 - 3
	0-2.5 mg	3 - 3.5
	0 mg	>3.5
Day 6	7.5 – 12.5 mg	< 1.5
	7.5– 10 mg	1.5 – 1.9
	5 mg or continue last dose	2 -2.5
	2.5-5 mg or continue last dose	2.5-3
	2.5 mg	3 – 3.5
	0 mg	>3.5

Initiation Anticoagulation Nomogram: Goal INR Range of 2.5-3.5

Target INR Goal of 2.5 -3.5		
Day	Warfarin Starting Dose (mg)	INR Value
Day 1	5 mg	<1.3
Day 2	5 mg	< 1.5
	2.5 mg	1.5 – 1.9
	0.5-1.25 mg	2 – 2.5
	0 - 1.25 mg	2.5 – 3
	0 mg	> 3
Day 3	5 – 10 mg	< 1.5
	2.5 – 5 mg	1.5 – 1.9
	2.5 mg	2 – 2.5
	1.25 - 2.5 mg	2.5 – 3
	1.25- 0 mg	> 3
Day 4	7.5- 10 mg	< 1.5
	5 – 7.5 mg	1.5 – 1.9
	2.5 – 5 mg or continue last dose	2 – 2.5
	2.5 – 5 mg	2.5 – 3
	1.25- 2.5 mg	3 - 3.5
	0 mg	> 3.5
Day 5	10 mg	< 1.5
	7.5 – 10 mg	1.5 – 1.9
	5 – 7.5 mg	2 – 2.5
	5 mg or continue last dose	2.5 – 3
	2.5 mg	3 – 3.5
	0- 1.25mg	>3.5
Day 6	7.5 – 12.5 mg	< 1.5
	7.5 – 10 mg	1.5 – 1.9
	5 – 7.5 mg	2 – 2.5
	5 mg	2.5 – 3
	2.5 -5 mg	3- 3.5
	0- 2.5 mg	>3.5

Initial dosing will be based on the estimated warfarin sensitivity, as described VII.1.1.2.

Make adjustment based on total weekly dose (Increase or decrease dose by 10% - 25% depending upon current INR and target INR)

Warfarin High Sensitivity patients include: baseline INR greater than 1.5, age greater than 65 years, hepatic disease, decompensated heart failure, malnourishment, malabsorption syndrome/chronic diarrhea, cancer, albumin less than 2 g/dL, thyrotoxicosis, debilitated, at high risk of bleeding, a genetic polymorphism of cytochrome P450 2C9 or patients who have undergone heart valve replacement.
Warfarin Moderate Sensitivity patients include: baseline INR 1.2 to 1.5, age 50-65 years old, or concurrent use of specified cytochrome P450 enzyme inhibitors.
Warfarin Low Sensitivity patients include: baseline INR less than 1.2, age less than 50 years old and no other sensitivity criterion.
Modified from: Trapskin, P.J. et al. *American Journal of Pharmaceutical Education*. 2005;69(2):190-197.

Day	Warfarin High Sensitivity†	Warfarin Moderate Sensitivity‡	Warfarin Low Sensitivity*
1	2.5 – 5 mg	5- 7.5 mg	10 mg

Appendix X: Risk Factors for Bleeding

- Age >75
- History of GI bleeding
- Hypertension
- History of stroke
- CHF
- Renal insufficiency

Appendix XI: Management of Elevated INR Associated with Bleeding

The recommendation guidelines from the ACCP (9th edition) are as follows:

Recommendation	
Bleeding or Urgent Surgery Required (with or without INR above therapeutic range)	
Serious or life-threatening bleeding at any elevation of INR or need for urgent surgery/invasive procedure (within 24 hrs)	Hold warfarin; give vitamin K 5-10 mg IV supplement with FFP or Factor VIIa (Novoseven) when FFP is ineffective. Repeat treatment as necessary.
Major but non-life-threatening bleeding with any increase in INR	Hold warfarin; give vitamin K 5-10 mg IV and consider supplemental FFP as necessary

Appendix XII: Stratification of Risk Factors for Thromboembolism

High risk for Thromboembolism:

- Hereditary hypercoagulable states:
  Factor V Leiden
  Antithrombin II deficiency
  Protein C. deficiency
  Protein S deficiency
  Antiphospholipid antibodies
- Recurrent VTE
- Venous or arterial thromboembolism within 3 months
- Rheumatic atrial fibrillation
- Mechanical valve replacement (3months)

Intermediate risk:

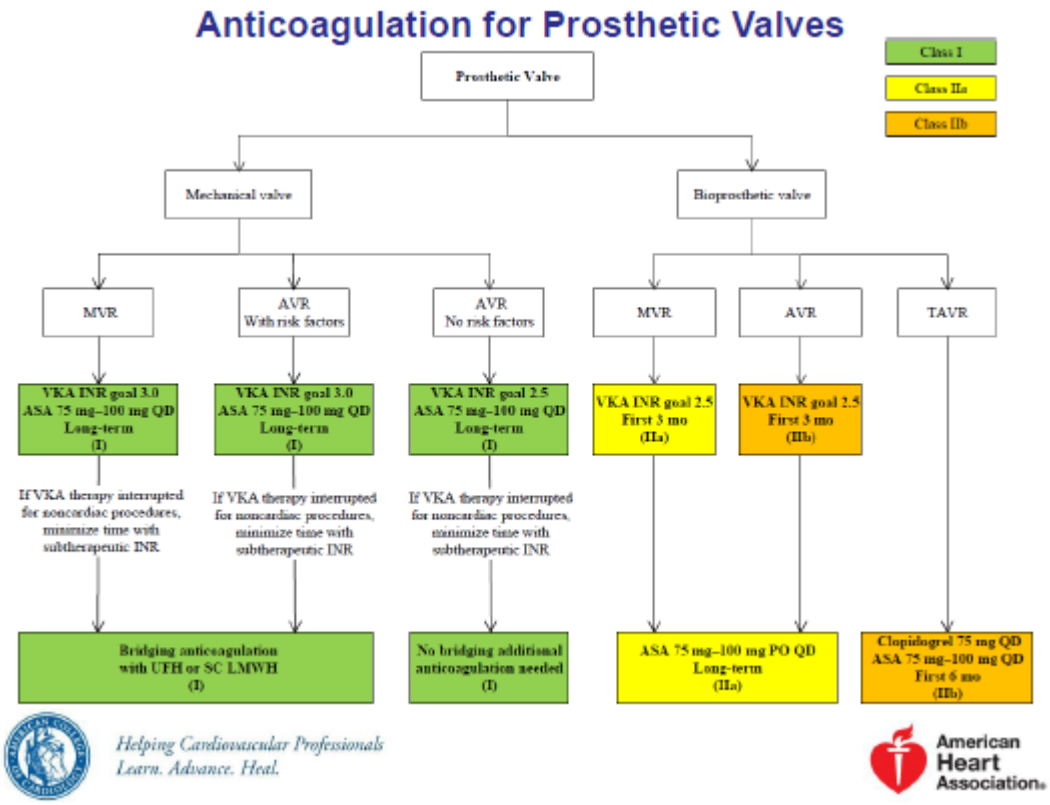
- Cerebrovascular disease with multiple strokes (2 or more) or TIA without risk factors for cardioembolism
- Venous thromboembolism >3-6 months
- Mechanical valves in aortic position
- Atrial fibrillation without a history of embolism, but with multiple risk factors for cardiac embolism.

Low risk:

- VTE > 6 months ago
- Intrinsic cerebrovascular disease without recurrent strokes or TIA
- Atrial fibrillation without multiple risk for cardioembolism

Appendix XIII: Anticoagulation management In Prosthetic Heart Valves

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease , Circulation. 2017;135:e1159–e1195



Adapted from Anticoagulation management In Prosthetic Heart Valves (AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease (2014)

Appendix XIV: Perioperative Management Before and After Dental Procedures

Management of anticoagulation before and after dental procedures requires careful, patient-specific evaluation of the risk of bleeding associated with the dental procedure as well as the risk of thromboembolism associated with the underlying disease state for which anticoagulation is indicated.
Patient specific management plans will be made in consultation with the dentist performing the procedure.

	Low Bleeding Risk	Moderate Bleeding Risk	High Bleeding Risk
Procedures	• Supragingival scaling • Simple restorations • Local anesthetic injections	• Subgingival scaling • Restorations with subgingival preparations • Standard root canal therapy • Simple extractions • Regional injection of local anesthetics	• Extensive surgery • Root removal • Alveolar surgery (bone removal) • Multiple extractions
Suggestions	• Do not stop taking warfarin. • Use local measures to prevent or control bleeding.	• Interruption of warfarin therapy is not suggested • Use local measures to prevent or control bleeding • Consult with dentist to determine comfort with use of local measures to	• May need to reduce INR or return to normal hemostasis. • Follow suggestions for "Preoperative Anticoagulation

		prevent bleeding.	Management” • Use local measures to prevent or control bleeding

Adapted from “Suggestions for management of anticoagulation therapy before and after dental procedures” from University of Washington Medical Center Anticoagulation Clinics.

Local Methods to Prevent or Control Bleeding

- Cold water rinse
- Local pressure (biting on gauze or tea bags)
- Site packing gelatin sponges (Gelfoam); absorbable oxycellulose (Surgicel); microcrystalline
- Additional suturing
- Electrocautery
- Tranexamic acid mouth rinse 5%
- Aminocaproic acid mouth rinse 5%:10ml in mouth for 2min just before dental procedure then repeat q2h for 6-10 doses prn (Amicar® 25 % oral solution).

Avoid Additional Bleeding Risks for 24 hours

- Hot liquids
- Mouth washes
- Hard foods
- NSAIDS and antiplatelet agents

Appendix XV: VTE Prophylaxis: LMWH to Warfarin Bridging Therapy

The ACCP 8$^{th/9th}$ edition guidelines recommend the following:

Elective total hip replacement	LMWH 30 mg SQ q 12h started either 12 h before or 12-24 h post op, or 40 mg SQ q24h. LMWH given for a minimum of 5 days and until INR goal achieved	Warfarin therapy (target INR 2-3) started the evening of the surgery. Warfarin recommended for minimum of 10 days and up to 35 days
Elective knee replacement	LMWH 30 mg SQ q 12h started either 12 h before or 12-24 h post op. LMWH given for a minimum of 5 days and until INR goal achieved	Warfarin therapy (target INR 2-3) started the evening of the surgery. Warfarin recommended for minimum of 10 days
Hip fracture	LMWH 30 mg SQ q 12h started either 12 h before or 12-24 h post op, or 40 mg q24h. LMWH given for a minimum of 5 days and until INR goal achieved	Warfarin therapy (target INR 2-3) started the evening of the surgery. Warfarin recommended for minimum of 10 days and up to 35 days

Appendix XVI: Anticoagulation Management Software: CoagClinic™

Examples of computerized reports:

- Patient Visit Summary Report
- Patient Progress Notes Report
- Patient Summary Report

- Quality Assurance Report

Appendix XVII: Contract with the Patient

Contract with the Patient

Your doctor has prescribed warfarin, an anticoagulant that helps prevent clot formation.
Anticoagulants, such as warfarin (Coumadin®), can save lives by preventing dangerous blood clots, but they carry the risk of unwanted bleeding.
The dosing of warfarin is very patient specific and requires frequent monitoring to ensure the safety and benefit of this drug.
It is important that we see you on a regular basis to check your warfarin blood level by testing your International Normalized ratio (INR).
The purpose of this contract is to ensure that you receive the best care and get the most benefit from this medication.

To accomplish this goal, we ask you to review the following list of expectations:

☐ Be present for each scheduled appointment and reschedule promptly if something prevents you from keeping an appointment

☐ Provide the Clinic with a current phone number and respond back to any messages left for you as soon as possible

☐ Accurately follow the Pharmacist's instructions about how much medication to take and when to take it

☐ Notify the Pharmacist of any changes in medications or diet, even if they occur between visits (including over the counter medications, vitamins and herbal remedies)

☐ Call the Clinic or your physician promptly if any signs or symptoms occur that may be related to warfarin (Coumadin ®), such as excessive bleeding.

My signature below constitutes my understanding and adherence to these expectations.

_____ _____
Patient Date

_____ _____
Pharmacist Date