Warfarin Clinical Practice Guideline
Care Process Model

Fast facts

- Warfarin is generally started on day 1 or 2 of heparin or low molecular weight (LMW) heparin therapy. Heparin or LMW heparin administration should overlap with warfarin for a minimum of 6 days and until INR (International Normalized Ratio) is within the desired therapeutic range on 2 consecutive days at least 24 hours apart when initiating warfarin therapy. In general, warfarin therapy should be initiated with consultation from hematology unless the patient is in a critical care unit or on the cardiology or cardiothoracic surgery service.
- Warfarin loading period is 4-7 days for most patients before a stable maintenance phase is achieved. Anticoagulation may be seen within 24 hours due to inhibition of factor VII but peak anticoagulation activity is not achieved for 72-96 hours due to factor II inhibition (2-3 days after 1st therapeutic INR is achieved).
- Warfarin inhibits thrombin formation by interfering with vitamin K metabolism. Age affects the degree of inhibition. Warfarin is rarely recommended for children < 2 months of age
- Available products at CMH:
  - Warfarin 1 mg, 2 mg, 4 mg and 5 mg tablets.
  - Doses should be rounded to the nearest 0.5mg wherever possible to allow for dispensing in tablet form.
  - Parents may be instructed to crush tablets, mix with water, measure dose and administer immediately if smaller increments are essential.
  - INR is calculated from the measured PT. If PT is ordered, INR will be calculated.
- **INR/PT** is used to monitor the effects of warfarin.

Indications

- Prophylaxis and treatment of venous thrombosis, pulmonary embolism, and thromboembolic disorders.
- Prevention of arterial thromboembolism in patients with mechanical prosthetic aortic and/or mitral valves or atrial fibrillation.

Initiation of therapy protocol - Days 1- 4

- Warfarin is generally started on day 1 or 2 of heparin or low molecular weight (LMW) heparin therapy. Heparin or LMW heparin administration should overlap with warfarin for a minimum of 6 days and until INR is within the desired therapeutic range on 2 consecutive days at least 24 hours apart when initiating warfarin therapy. In general, warfarin therapy should be initiated with consultation from hematology unless the patient is in a critical care unit or on the cardiology or cardiothoracic surgery service.
- **Target INR (International Normalized Ratio):**
  - **2.5 to 3.5** for patients with **mechanical/prosthetic mitral valves or recurrent thrombotic events with a therapeutic INR.**
  - **2.0 to 3.0** for all other patients including patients with mechanical aortic valves.
- Obtain blood for baseline INR/PT, aPTT.
- Calculate **initial (day 1) warfarin dose** based on weight, co-morbidities and baseline INR.
  - Patient with a baseline INR < 1.2 and no liver or Fontan co-morbidities or hemorrhagic risk:
    - 0.2 mg/kg PO as a single dose.
    - Maximum 10 mg.
  - Patient with a baseline INR ≥ 1.2 - Consult Hematology.
  - Patient with liver dysfunction, Fontan procedure, presence of other hemorrhagic risk (hemodialysis):
    - 0.1 mg/kg PO as a single dose.
    - Maximum dose 5 mg.
- Obtain daily INR during initiation protocol.
- Calculate subsequent (**days 2-4 only**) warfarin initiation doses based on the INR response (see Table 3).

Table 3. Adjusting Warfarin Dose for Days 2 to 4 ONLY

INR	**Warfarin Adjustment**
1.1-1.3	repeat initial loading dose
1.4-3	50% of initial loading dose
3.1-3.5	25% of initial loading dose
> 3.5	hold until INR < 3.5; restart at 50% of previous dose

Continuation of therapy - Day 5 forward

- **Target INR** for patients **who have completed Day 1 through 4 of the initiation protocol**
  - **2.5 to 3.5** for patients with **mechanical /prosthetic mitral valves or recurrent thrombotic events**
  - **2 to 3** for **all other patients including mechanical/prosthetic aortic valves**
- **Adjust warfarin dose from day 5 forward** based on INR response
  - **Medically stable patients without** mechanical mitral valves or recurrent thrombotic events - **target 2 to 3** (see Table 4):

Table 4. Adjusting Warfarin Dose for Days 5 forward for **Medically Stable Patients *Without*** Mechanical Mitral Valves or Recurrent Thrombotic Events

INR	**Warfarin Adjustment**
1.1-1.4	increase dose by 20%
1.5-1.9	increase dose by 10%
2-3	no change
3.1-3.5	decrease dose by 10%
>3.5	hold until INR <3.5; restart at 20% less than the previous dose

- **Mechanical /prosthetic mitral valves or recurrent thrombotic events - target 2.5 to 3.5** (see Table 5):

Table 5. Table 4. Adjusting Warfarin Dose for Days 5 forward for **Mechanical /prosthetic Mitral Valves or Recurrent Thrombotic Events**

INR	**Warfarin Adjustment**
1.1-1.4	increase dose by 20%
1.5-2.4	increase dose by 10%
2.5-3.5	no change
>3.5	hold until INR <3.5; restart at 20% less than the previous dose

Maintenance and monitoring

- Target INR (International Normalized Ratio) is 2 to 3 for most patients. Children with mechanical/prosthetic mitral valves or recurrent thrombotic events as described above should have a target INR between 2.5-3.5
    - Discontinue heparin/LMW heparin once the INR is >2 for 2 consecutive days **and** at least 6 days of heparin/LMW heparin have been given. Anticipate a small decline in INR the following day.
- INR/PT monitoring recommendations:
    - Obtain baseline before initiating warfarin therapy.
    - Obtain daily INR/PT until therapeutic range has been reached and sustained for 2 consecutive days (loading INR/PT monitoring protocol complete).
    - Obtain INR/PT within 3 days of discharge from the hospital.
    - Obtain INR/PT 5-7 days after initiating a new dose.
    - Once a stable INR between 2-3 (2.5-3.5 for mechanical/prosthetic mitral valves) has been noted on **two INRs taken 7 days apart** INRs may be obtained **weekly**. When stable for 4 to 8 weeks, then go to INR every 2-4 weeks.
    - Recommend monitoring at least once a month when stable.
- Duration of therapy:
    - DVT with an underlying cause: 3 months, with possible extension based on clinical situation; consult Hematology.
    - Idiopathic DVT: 6 -12 months.
    - Mechanical heart valves - indefinite.
    - Recurrent thromboembolic events - indefinite.
    - Antiphospholipid antibody syndrome - indefinite.

Dietary considerations

- Patients/Parents should notify physician for:
    - Significant changes in diet with foods high in Vitamin K:
        - Kale, spinach, broccoli, cauliflower, turnip greens, chick peas, brussel sprouts, green tea, soybean oil, liver (beef, pork, or chicken), soy protein products (including tofu), and vitamins A and E in large doses.
        - If the patient's diet already contains these foods, **Don't Change Eating Habits**. Consistency in the daily eating pattern is key. If any of these foods are routinely consumed, adjust the medication (Warfarin) rather than adjusting the diet.
    - Be aware of Vitamin K when changing from breast feeding to formula.
        - Breast milk averages 4mcg/L of vitamin K, formula averages 50mcg/L of vitamin K.
        - Specialized protein hydrolysate formulas may contain higher levels of vitamin K.
- CMH inpatients will have education on consistency in eating habits. Vitamin K controlled diet will be ordered to ensure consistency of vitamin K content in food while on inpatient status.
- Patients with vitamin K in TPN before or as warfarin therapy begins:
    - Establish warfarin dosing based on TPN with vitamin K included.

- Pediatric multi-vitamin product contains vitamin K (200 mcg/5 mL); removing from TPN puts patient at risk for other vitamin deficiencies.
- Gastrointestinal illness or change in diet can affect INR.

Potential drug interactions

- **Loading dose** should be decreased by 25% for patients receiving amiodarone.
- Drug interactions with warfarin may occur via several mechanisms, including impairment of absorption, induction or inhibition of metabolism, competition for protein-binding sites, and platelet inhibition. Drugs that inhibit or induce P-450 2C9 (responsible for metabolism of S-warfarin) may have the greatest effect on INR.
- Complementary/alternative medications known to have potential to *increase* warfarin effects include bromelains, danshen, dong quai, garlic, gingko biloba, ginseng and omega 3 fish oil.
- Complementary/alternative medications known to have potential to *decrease* warfarin effects include CoQ10 and St. John's Wort.
- INR should be monitored more frequently in pediatric patients who are already on warfarin therapy and are starting on antibiotics.
- Warfarin dosing can be adjusted to permit use of some medications that have an effect on warfarin metabolism. Please consult Hematology for adjustment recommendations.

Table 6. Commonly used Drugs in Children that affect INR Values

Drug	INR Effect	Mechanism
Amiodarone	Increase	Decreases warfarin metabolism
Antifungal agents	Increase	Fluconazole, ketoconazole, and miconazole (vaginal) decrease warfarin metabolism
Barbiturates	Decrease	Increase warfarin metabolism
Carbamazepine	Decrease	Increase warfarin metabolism
Cephalosporins	Increase	Inhibits production of vitamin K dependent clotting factors
Ciprofloxacin	Increase	Displace warfarin from binding sites (possible mechanism; not fully known)
Clarithromycin	Increase	Decrease warfarin metabolism
Contraceptives (Oral)	Increase	Increase clotting factor synthesis; may inhibit oxidative metabolism
Corticosteroids	Increase	Produce hypercoagulability; may have ulcerogenic effects
Delaviridine	Increase	May inhibit warfarin metabolism
Erythromycin	Increase	Decrease warfarin metabolism
Ibuprofen	Increase	May inhibit warfarin metabolism in addition to platelet inhibition
Indomethacin	Increase	May inhibit warfarin metabolism in addition to platelet inhibition
Isoniazid	Increase	May inhibit warfarin metabolism
Losartan	Increase	May inhibit warfarin metabolism
Omeprazole	Increase	May inhibit of warfarin metabolism
Metronidazole	Increase	Inhibits metabolism of S-isomer
Nicardipine	Increase	May inhibit warfarin metabolism
Pantoprazole	Increase	May inhibit warfarin metabolism

Penicillins	Increase	May enhance warfarin metabolism; May reduce GI flora synthesis of vitamin K
Phenytoin / fosphenytoin	Decrease	Increase warfarin metabolism; induces warfarin metabolism; displaces warfarin from protein-binding sites; enhances metabolism of clotting factors
Rifampin	Decrease	Induces hepatic enzymes, increases warfarin metabolism
Sulfamethoxazole - Trimethoprim (Bactrim)	Increase	Sulfonamide component may stereo-selectively inhibit S-isomer metabolism
Vitamin K (ADEK, Centrum, Viactiv)	Decrease	Effects of oral anticoagulants are directly antagonized by the excessive ingestion of foods or dietary supplements containing vitamin K
Zafirlukast	Increase	May inhibit warfarin metabolism

Other important interactions		
Drug	**Effect**	**Mechanism**
Aspirin, NSAIDs	Increased risk of bleed	Inhibition of platelet aggregation
Anti-platelet agents (dipyridamole, clopidrogel, ticlopidine, cilostazol)	Increased risk of bleed	Inhibition of platelet aggregation

Adverse effects

- Bleeding
  - Most common adverse effect
- Skin rash and alopecia
  - Uncommon
- Skin necrosis
  - Rare, often seen with Heparin Induced Thrombocytopenia (HIT).
  - Occurs due to inadequate anticoagulation with heparin or LMW heparin while initiating warfarin.
  - Ensure 2 INRs > 2 prior to stopping heparin or LMW heparin for prevention of HIT.
  - Investigate for deficiencies in Protein C and S
- Osteopenia
  - Rare

Warfarin antidotes

- Antidotes:
  - Vitamin K (phytonadione)
  - Kcentra
  - FFP (fresh frozen plasma)
- Choice and dose is dependent on the clinical problem-no bleeding vs. significant bleeding and need for future warfarin therapy.
- **If patient requires rapid warfarin reversal but has no bleeding, insignificant bleeding or bruising:**
  - **Vitamin K 30 mcg/kg by slow IV infusion over 10-20 minutes** (to avoid anaphylaxis). Max dose **2 mg.**
    - This weight adjusted regimen is safer for pediatric patients than a universal dosage (i.e. 0.5-2mg) as recommended for adults. Even 0.5mg (sufficient for many adults) is likely to be too high for most young children. Seriously ill children with liver dysfunction may require more than a single dose. Oral vitamin K is effective in adults but the INR fall is slower than IV injection.
  - The **preferred route is IV**, but in a child with **poor or no venous access, the PO or SQ route may be used**, particularly if the INR is 6-10. The PO route is preferred.
  - The IM route is NOT recommended.
- **If patient has significant bleeding:**
  - Not life threatening and will not cause morbidity:
    - **Vitamin K 30 mcg/kg by slow IV infusion over 10-20 minutes** (to avoid anaphylaxis). Max dose **2 mg.**
    - **Kcentra**
      - Administer with vitamin K concurrently
      - Dosing based on pretreatment INR:

Pretreatment INR	Dose (in units of factor IX activity)	Maximum Dose
2 to <4	25 units/kg	2500 units
4 to 6	35 units/kg	3500 units
>6	50 units/kg	5000 units

      - Check INR stat 30 minutes after end of Kcentra infusion
        - If INR<1.5, proceed with procedure
        - If INR>1.5 or bleeding not controlled, contact the Coagulation Consult Service immediately
    - **Consider FFP 20 mL/kg IV.**
  - Life threatening and will cause morbidity:
    - **Vitamin K 30 mcg/kg IV by slow IV infusion over 10-20 minutes** (to avoid anaphylaxis). Max dose **5mg.**
    - **And FFP 20 mL/kg IV.**
    - **Kcentra**
      - Administer with vitamin K concurrently
      - Dosing based on pretreatment INR:

Pretreatment INR	Dose (in units of factor IX activity)	Maximum Dose
2 to <4	25 units/kg	2500 units
4 to 6	35 units/kg	3500 units
>6	50 units/kg	5000 units

        - Check INR stat 30 minutes after end of Kcentra infusion
            - If INR<1.5, proceed with procedure
            - If INR>1.5 or bleeding not controlled, contact the Coagulation Consult Service immediately
    - Consider giving **NovoSeven RT 90 micrograms/kg IV** (alternate choice).
- **Safety of IV administration**
    - The standard product for IV administration of Vitamin K at CMH is the 2mg/mL concentration, which is readily available in medication stations on every inpatient unit.
    - This dilute form (2mg/mL) along with slow IV infusion over 10 to 20 minutes may avoid anaphylaxis that has been associated with IV administration of vitamin K.
    - Where the concentrated 10mg/mL product is available, it must be diluted to 2mg/mL with D5W or NS prior to administration.

Other considerations

- Avoid arterial punctures.
- Hold warfarin for 2 doses prior to minor procedures, then restart usual dose of warfarin the following day.
- Avoid aspirin, NSAIDs and other antiplatelet drugs unless required for specific disease management or clinical situation.
- Consider alternative analgesics such as acetaminophen or choline magnesium trisalicylate (Trilisate®), as clinically appropriate, if analgesia is required.
- No contact sports - but other normal activities are allowed.
- Pregnancy
    - Warfarin should be used cautiously due to its potential teratogenic effects on the fetus.
    - Teenagers need to receive appropriate counseling.
    - Enoxaparin (Lovenox®) or other low molecular weight heparin is the treatment of choice for teens that require anticoagulation during pregnancy.
- Surgery/invasive procedures:
    - Discontinue warfarin 5 days prior to surgery/invasive procedures unless the clinical situation requires an emergent intervention. For conditions necessitating more emergent intervention consult hematology.
    - Resume warfarin and heparin or LMW heparin 12 to 24 hours after surgery/invasive procedure. Continue the heparin or LMW heparin until the INR is therapeutic for 2 consecutive days.
    - Patients with mechanical/prosthetic mitral valves, atrial fibrillation or recent/recurrent thromboembolism require bridging with standard heparin or low molecular weight heparin. Consult hematology or cardiology (for specifically cardiac related problems).
- Patients should consult physician for the following:
    - Significant changes in diet, formula intake for infants.
    - Introduction of new medication (e.g. antibiotics) and any over-the-counter (OTC) medication.
    - Changes in doses of on-going medications.
    - Infections.
    - Diarrhea and vomiting.

Indications for Hematology consultation

- Initiation of therapy for patients
  - Not in critical care unit
  - Age < 30 days
  - Baseline INR ≥ 1.2 prior to initiation of warfarin
  - Impaired renal function
- Maintenance of anticoagulation therapy with
  - Delay in reaching therapeutic anticoagulation
  - Progression of thrombus
  - Concern for heparin induced thrombocytopenia (HIT)
  - Hemorrhage and need for antidote
- Surgery or invasive procedure in patients with
  - Mechanical/prosthetic mitral valves
  - Atrial fibrillation
  - Recent/recurrent thromboembolism
- Use of LMW heparin other than enoxaparin

Patient education

- Do NOT switch manufacturers of warfarin.
- CMH Inpatients:
  - Direct patient education on warfarin will be provided by CMH pharmacists for CMH inpatients. Education and documentation of education provided will include:
    - Food, drug and complementary/alternative medication interactions with warfarin, signs of bleeding, importance of lab work, importance of informing all health care providers of use of warfarin, and recommendation for use of a Med ID/alert bracelet.
  - Direct patient education and patient educational materials emphasizing consistent intake of Vitamin K in the diet will be distributed to patients.
- CMH Outpatients:
  - Patient counseling and written materials on warfarin will be provided by the CMH Outpatient Pharmacy on receipt of prescriptions.
  - Lexicomp patient leaflets are available to outpatient clinics for patients who will obtain prescriptions from sources other than the CMH Outpatient Pharmacy.

Genotyping

CYP2C9 and VKORC1 genotype results may provide directional guidance for warfarin dosing in pediatric patients. Clinical genotyping is available through the CMH Laboratory. Approximately 50% of the variability in warfarin dose-response in adults has been associated with the variants in CYP2C9 and VKORC1 detected by this test. The test does not provide quantitative information which links a specific genotype with a precise warfarin dose and large scale studies looking at genotype and effect have not been performed; however, the results may be useful in clinical decision making when interpreted in the context of other "factors" known to influence the dose-response for warfarin (such as drug-drug interactions, patient age, drug-diet interactions, drug-disease interactions). Consultations provided by the Division of Pediatric Clinical Pharmacology and Medical Toxicology can provide such a multifactorial assessment and thus, may be beneficial.

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