CLINICAL PRACTICE GUIDELINES

Initiation and Maintenance of Warfarin (Coumadin) In patients ≥10 kg

Disclaimer: ***These clinical practice guidelines are based upon the opinions of staff members of The Children's Hospital of Philadelphia. Treatment should be individualized and based upon the clinical conditions of each patient***

General Information

These guidelines apply to the use of warfarin for the treatment and prevention of thromboembolic disorders.

Warfarin is a well-established anticoagulant for long-term prevention of thromboembolism. The pharmacology is markedly different in children compared to adults.

Baseline Monitoring (To be completed prior to initiating warfarin)

Baseline labs are to be completed to ensure patient has a normal baseline coagulation state:

- PT/INR
- PTT
- CBC
- Baseline urine pregnancy test in menstruating females

If the patient has abnormal coagulation studies, thrombocytopenia or is pregnant, the hematology team should be consulted.

Dosing

Initiation

- In general, patients with acute thrombosis or known protein C or S deficiency should already be anticoagulated (achieved therapeutic levels) with either unfractionated heparin (uFH) or low molecular weight heparin (LMWH) prior to starting warfarin.
- Warfarin is thought to achieve pro-coagulant effects (reduction of Vitamin K dependent factors with shorter half-lives; lowers proteins C/S first) prior to achieving anticoagulant effects (reduction of the prothrombin, which has a 60 – 72 hour half-life), making a period of overlap between therapeutic uFH/LMWH levels and INRs prior to stopping uFH/LMWH. This period of overlap is generally 3-5 days at minimum and at least 2 therapeutic INRs at approximately 24 hours apart are recommended before discontinuation of uFH/LMWH.

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Table 1. Protocol for Oral Anticoagulation Therapy to Maintain an INR between 2 and 3 for Pediatric Patients*

Protocol	Action
I. Day 1: if baseline INR is 1– 1.3	Dose 0.2 mg/kg x1 PO
II. Loading days 2–4	
INR 1.1–1.3	Repeat initial loading dose
INR 1.4–1.9	50% of initial loading dose
INR 2–3	50% of initial loading dose
INR 3.1–3.5	25% of loading dose
INR > 3.5	Hold until INR < 3.5 then restart at 50% of previous dose
III. Maintenance oral anticoagulation dose guidelines	
INR 1.1–1.3	Increase by 20% of dose
INR 1.4–1.9	Increase by 10% of dose
INR 2–3	No change
INR 3.1–3.5	Decrease by 10% of dose
INR > 3.5	Hold until INR < 3.5 then restart at 50% of previous dose

Table 2. Protocol for Oral Anticoagulation Therapy to Maintain an INR between 2.5 and 3.5 for Pediatric Patients*

Protocol	Action
IV. Day 1: if baseline INR is 1– 1.3	Dose 0.2 mg/kg x1 PO
V. Loading days 2–4	
INR 1.1–1.3	Repeat initial loading dose
INR 1.4–1.9	50% of initial loading dose
INR 2–3	50% of initial loading dose
INR 3.1–4	25% of loading dose
INR > 4	Hold until INR < 3.5 then restart at 50% of previous dose
VI. Maintenance oral anticoagulation dose guidelines	
INR 1.1–2	Increase by 20% of dose
INR 2-2.4	Increase by 10% of dose
INR 2.5–3.5	No change
INR 3.6–4.5	Decrease by 10% of dose
INR 4.6–5	Decrease by 20% of dose
INR > 5	Hold until INR < 5 then restart at 20% of previous dose

- For patients transitioning from uFH to warfarin in the hospital, it is faster to use a loading dose of warfarin see algorithm to the left. **Note: Max loading dose 10 mg.**
- Patients who have had a Fontan procedure or have Liver disease are generally more sensitive to warfarin, and so a conservative **loading dose of 0.1 mg/kg** is recommended.
- Patients under the age of 1 year often require much higher doses of warfarin. Please consult the anticoagulation monitoring team (via pharmacy) for assistance with these patients.
- An alternative approach to initiating patients on warfarin as an inpatient or, more commonly, as an outpatient without a loading dose is described below.

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- **Alternatve Dosing**This approach has been used by CHOP hematology and while not validated, has been successful and requires less frequent monitoring:
  - The starting dose of warfarin can be approximated, based on age and weight
    - Age 2-12 yrs: 0.09 mg/kg day
    - Age >12yrs: 0.08 mg/kg day
    - You should choose a dose that is a whole number.
  - Continue heparin and warfarin for 5 days
  - Check INR on day 5
  - If the INR is therapeutic, stop the heparin (uFH or LMWH) – check INR in 3-5 days. If day 5 INR is subtherapeutic, increase warfarin (see Table 1 or 2 above, section III Maintenance) and continue heparin (uFH or LMWH) until INR is therapeutic.
  - See below for ongoing monitoring recommendations.

Intensity (Target INR)

- The target INR for children is extrapolated from studies and recommendations for adult patients. While the choice of target INR will depend upon the indication and the risk of bleeding and thrombosis particular to each patient, for most indications, the target INR is 2.5 (range 2-3).
- In rare exceptions, such as patients with caged ball or caged disk valves, or tilting disk valves and bi-leaflet mechanical valves in the mitral position, possibly patients with antiphospholipid antibody syndrome, and patients with recurrent venous thromboembolism despite therapeutic INRs, higher target INRs have been suggested (e.g. INR of 3 for certain mechanical valves and up to 4 for antiphospholipid syndrome). The evidence to support higher INR thresholds is limited and the risk for bleeding complications is increased.
- Warfarin generally is not recommended for primary or secondary prophylaxis for central venous lines associated thrombosis, particularly in cancer patients.

Monitoring

- Once the patient has reached a therapeutic INR, the INR should be checked at least 1x/wk for 2-3 weeks as an outpatient, to document and establish a stable INR and dose. Once a stable dose and INR is achieved, then the INR should be checked every 2 weeks for a period of time. If no dose changes are made, some patients may be monitored at longer intervals (every 3-4 weeks); though this decision should be carefully considered in each case, based on historical data and safety.
- See Table 1 or 2 above for adjustments to maintenance warfarin dose when the INR is not in the therapeutic range.
- In addition, the INR should be checked with any change to the patient's medications, dietary

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vitamin K intake (if patient made NPO, for instance), GI absorption (if patient has gastrointestinal symptoms such as with gastroenteritis, for instance), prolonged antibiotics, systemic steroid, or hepatic function.

- There are numerous medications/foods that will either decrease or increase anticoagulation effects of warfarin. **Upon prescribing new medications, physicians should always check with the CHOP Formulary or Pharmacy (x42030) to determine potential interactions and monitor patients accordingly.** Patients should maintain a consistent diet of foods containing vitamin K. These foods rich in vitamin K include: asparagus, broccoli, brussel sprouts, cabbage, cauliflower, egg yolk, kale, lettuce, potatoes, spinach, turnip greens, vegetable oils, and watercress. Patients should avoid foods that have anticoagulant properties. Herbs with anticoagulant properties include: dong quai, fenugreek, feverfew, garlic, ginger, ginkgo, and ginseng.
- Several genetic polymorphisms have been associated with warfarin sensitivity in patients. Screening for genetic variants is not available for most situations.
- Pregnancy status should be assessed in patients of childbearing age, because **warfarin is a teratogen**

Management of Supratherapeutic INR

- Patients on warfarin for a prosthetic valve, may be at increased risk for thrombi or warfarin resistance if administered vitamin K, and cardiology should be contacted regarding therapy for these patients
- See Table 2 below for details:

Table 3. Recommendations for Managing Supratherapeutic INR (adapted from Chest guidelines)

Condition	Management
INR above therapeutic range but < 5; no significant bleeding	Lower dose or omit dose, monitor more frequently -(in 2-3 days) and resume at lower dose when INR therapeutic; if only minimally above dose range, no dose reduction may be necessary
INR > 5 but < 9; no significant bleeding	Omit next one or two doses. Monitor more frequently and resume at lower dose when INR in therapeutic range.
INR > 9; no significant bleeding	Hold warfarin therapy and: • Prosthetic valve patients – Discuss with cardiology • DVT/PE patients – Vitamin K (2.5 mg orally) with the expectation that the INR will be substantially reduced in 24-48 hr.

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	Resume therapy at lower dose with INR therapeutic
Serious bleeding at any INR	Prosthetic valve – FFP 15 ml/kg, repeat as necessary. DVT/PE – Hold warfarin and give 1 mg vitamin K IV by slow (see below) continuous infusion and FFP (15 ml/kg– repeat as necessary); vitamin K can be repeated in 12 hours; rVIIa can be considered as an alternative if FFP volume is limiting, though considered carefully as it may increase risk of thrombosis.

The optimal route and dose of vitamin K for reversal in children is dependent on patient condition. The IV route is recommended in urgent situations given the more predictable absorption, but must be given slowly (over 30-60 min.) because of the risk of anaphylactic shock. **Oral administration is the preferred route in young children.** Subcutaneous dosing can be used but is not established as superior to oral dosing.
IM injections are never indicated.

Warfarin reversal for elective procedures

This depends on the perceived risk of thrombosis when the patient is not anticoagulated. Patients with cardiac valves are at high risk, and need to be covered with heparin as the warfarin wears off. Other patients, on chronic therapy, who are more low risk, may be able to stop their warfarin 3-5 days prior to a procedure and restart home dose or bolus with 1.5–2x home dose for 1-2 days then resume home dose, without overlap with heparin. This should not be done in patients with Protein S or Protein C deficiency because of the risk of skin necrosis. **Please consult the Hematology thrombosis team, as this should be individualized**.

The effectiveness of administered Vitamin K can be monitored by INR. The effect has been seen at 4-6 hours after IV administration. For adults, a reduction in INR is apparent within 12-24 hours after oral administration.

Note that high doses of vitamin K can lead to warfarin resistance for 1 week, and therefore, the need for additional anticoagulation in the short term should be considered. Additional short-term anticoagulation with heparin should be considered. Note also that the half-life of warfarin is 36-42 hours and that it is metabolized via the liver.

Complication

- The attending physician of record or the attending defined responsible for outpatient management will be responsible for the diagnosis and management of any potential complications (i.e. bleeding, etc) in consultation with the division of hematology as deemed appropriate.

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- Reporting of complications, including bleeding requiring transfusion, intracranial hemorrhage, and over-anticoagulation requiring reversal, into the electronic reporting system, Safety Net, is highly recommended.

Education

- Prior to discharge, all patients and their families should receive education regarding the safe use of warfarin. There are educational booklets on Warfarin available through Hematology, Cardiology and the Connelly Center and on the CHOP intranet as a patient/family pdf.
- All patients discharged on warfarin should have a follow-up appointment, including date and time scheduled for outpatient follow-up **(including INR within one week)**, at the time of discharge. In addition, the attending physician who will be responsible for outpatient management of the enoxaparin will be identified and documented.