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Management of Warfarin Therapy

Clinical Question

P (population/problem): In patients at a pediatric institution requiring long-term systemic anticoagulation with warfarin,
I (intervention): what are the appropriate medication doses and laboratory monitoring parameters
O (outcome): to prevent under-coagulation and over-anticoagulation complications?

Target Population

Inclusion: Patients receiving warfarin therapy at a pediatric institution

Exclusion: Children less than 3 months of age
Patients receiving hemodialysis for renal failure

Recommendations (See Table of Recommendation Strength following references)

Laboratory Monitoring

Laboratory Studies required for warfarin therapy

1. It is recommended that the International Normalized Ratio (INR) be used as the standard laboratory measurement for the management of warfarin therapy (*Ansell 2008 [5a]*).

Note 1: The INR is defined as: (patient prothrombin/mean normal prothrombin time)^{ISI}. ISI stands for International Sensitivity Index and denotes the ISI of the thromboplastin used at the local institution to measure the prothrombin time (PT) (*Ansell 2008 [5a]*).

Note 2: The ISI reflects the responsiveness of a given thromboplastin to the reduction of the vitamin K-dependent coagulation factors compared with the World Health Organization (WHO) standard value (*Ansell 2008 [5a]*).

Note 3: Patients with lupus anticoagulants with an elevated INR cannot be adequately measured by the INR. Direct monitoring of factor X levels is necessary (*Ansell 2008 [5a]*).

Therapeutic INR Values

2. It is recommended to maintain an INR range of 2.0 to 3.0 in most patients (*Ansell 2008 [5a]*).
Note: A normal INR in patients not receiving warfarin therapy is 1.0 (*Ansell 2008 [5a]*).
3. It is recommended to maintain an INR range of 2.5 to 3.5 in patients with a mechanical heart valve (*Ansell 2008 [5a]*).

Baseline Laboratory Studies

4. It is recommended to obtain the following laboratory studies prior to the start of warfarin therapy:
 - Complete Blood Count (CBC) with differential
 - INR
 - Activated partial thromboplastin time (aPTT)
 - Liver function tests (ALT, AST, total and direct bilirubin, alkaline phosphate)(*Ansell 2008 [5a]*).
5. It is recommended to consider ordering warfarin pharmacogenetic testing prior to the start of therapy (*Ansell 2008 [5a]*).
Note 1: For pediatric patients (< 20 years) beginning to use warfarin, there is no evidence-based algorithm that incorporates genetic information for dosing (*Local Consensus [5]*).

Note 2: For adult patients (≥ 20 years) beginning to use warfarin, there are evidence-based algorithms that incorporate genetic and clinical information for dosing recommendations. One such algorithm can be found at: <http://www.warfarindosing.org> (Ansell 2008 [5a]).

6. It is recommended prior to the initiation of warfarin therapy to consider obtaining blood for the evaluation of thrombophilic disorders and other tests (for example, fibrinogen, D-dimer, fibrin split products), as clinically indicated (Ansell 2008 [5a]).

Maintenance Laboratory Monitoring

7. It is recommended to measure the INR within 3 days of discharge from the hospital (Local Consensus [5]).
8. It is recommended to always draw an INR 5 to 7 days after initiating a new dose (Ansell 2008 [5a]).
 - When 2 INRs taken 5 to 7 days apart are stable, the interval for checking the INR can be expanded to two weeks
 - When again stable, expand to 3 weeks
 - When again stable, expand to 4 weeks

Stable is defined as the patient achieving two consecutive INRs between 2.0 and 3.0 (or 2.5 to 3.5 for mechanical heart valves) (Ansell 2008 [5a]).

9. It is recommended to monitor the INR a MINIMUM of once every 4 weeks (Ansell 2008 [5a]).

Note: Consider increased monitoring of warfarin therapy in children less than 2 years of age, secondary to their age and the potential for drug-nutrient interactions with formula and/or breast milk (Monagle 2008 [5a]).

Dosing

Initial Dose

10. It is recommended to start warfarin orally as a single daily dose in the evening as described in Table 1 (Ansell 2008 [5a], Monagle 2008 [5a]).

Note: Cincinnati Children’s Hospital Medical Center (CCHMC) provides multiple tablet strengths of warfarin. Prescribe doses as combinations of available tablet strengths whenever possible.

Table 1: Warfarin Initial Dose* (Ansell 2008 [5a], Monagle 2008 [5a])

Age	Population	Starting dose	Frequency	Max daily dose
3 months to 18 years	Children	0.2 mg/kg	once daily in the evening	10 mg
	Children with liver dysfunction or Following a Fontan procedure	0.1 mg/kg	once daily in the evening	5 mg
18 years of age and older	Adults	5 to 10 mg	once daily in the evening	10 mg

*If the baseline INR is ≥ 1.2 , reduce the initial loading dose to 0.1 mg/kg (Monagle 2008 [5a]).

Maintenance Dosing and Monitoring

11. It is recommended to start monitoring INR levels daily after the second dose of warfarin therapy based on the INR response as described in Table 2 (Ansell 2008 [5a], Monagle 2008 [5a]).

Table 2: Warfarin maintenance dose adjustment based on INR of 2.0 to 3.0*(Ansell 2008 [5a], Monagle 2008 [5a])

Day of warfarin therapy	INR level	Oral warfarin dose
Day 2 to 4	INR 1.1 to 1.3	Repeat initial loading dose
	INR 1.4 to 3.0	Decrease dose by 50% of the initial loading dose
	INR 3.1 to 3.5	Decrease dose by 75% of the initial loading dose
	INR > 3.5	Hold until INR <3.5 then restart at 50% of previous dose
Day 5 and maintenance	INR 1.1 to 1.4	Increase dose by 20%
	INR 1.5 to 1.9	Increase dose by 10%
	INR 2.0 to 3.0	No change
	INR 3.1 to 3.5	Decrease dose by 10%
	INR > 3.5	Hold until INR < 3.5, then restart at 80% of the previous dose

*Adjust dosing accordingly in patients with mechanical valves requiring the INR to be maintained between 2.5 and 3.5 (Ansell 2008 [5a]).

Managing patients with elevated INRs or bleeding

12. It is recommended that vitamin K be used to reverse the effects of warfarin. Use intravenous doses of vitamin K of 30 micrograms/kg in children and younger adolescents (Ansell 2008 [5a], Monagle 2008 [5a]).
- If continued warfarin therapy is indicated after high doses of vitamin K, then unfractionated heparin or LMWH can be given until the effects of vitamin K have been reversed and the patient becomes responsive to warfarin therapy (Ansell 2008 [5a]).
13. It is recommended to manage elevated INRs or bleeding in older adolescent and adult patients receiving warfarin as noted in Table 3 (Ansell 2008 [5a]).

Table 3: Recommendations for managing elevated INRs or bleeding in older adolescents and adult patients receiving warfarin (Ansell 2008 [5a])

Condition	Description
INR above therapeutic range but < 5; no significant bleeding	<ul style="list-style-type: none"> • Lower dose or hold dose • Monitor more frequently • Resume at lower dose when INR therapeutic • If only minimally above therapeutic range, no dose reduction may be required
INR ≥ 5 but < 9 with no significant bleeding	<ul style="list-style-type: none"> • Hold next one or two doses • Monitor more frequently • Resume at lower dose when INR in therapeutic range • Alternatively, hold one dose and give vitamin K (5 mg orally) particularly if at increased risk of bleeding • If more rapid reversal is required because the patient requires urgent surgery, vitamin K (2.5 to 5 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 hours • If INR is still high after 24 hours, additional vitamin K (2.5 mg orally) can be given
INR ≥ 9 with no significant bleeding	<ul style="list-style-type: none"> • Hold warfarin therapy • Give higher dose of vitamin K (5 to 10 mg orally) with the expectation that the INR will be reduced substantially in 24 to 48 hours • Monitor more frequently • Use additional vitamin K if necessary after 24 to 48 hours • Resume therapy at lower dose when INR therapeutic
Serious bleeding at any elevation of INR	<ul style="list-style-type: none"> • Hold warfarin therapy • Give vitamin K (10 mg by slow IV infusion), supplemented with fresh plasma (15 to 20 ml/kg) and/or recombinant factor VIIa (Novoseven®) at 20 to 90 mcg/kg IV over 3 to 5 minutes • Vitamin K can be repeated every 12 hours depending on the INR
Life-threatening bleeding	<ul style="list-style-type: none"> • Hold warfarin therapy • Give vitamin K (10 mg by slow IV infusion), supplemented with fresh plasma (15 to 20 ml/kg) and/or recombinant factor VIIa (Novoseven®) at 20 to 90 mcg/kg IV over 3 to 5 minutes • Vitamin K can be repeated every 12 hours depending on the INR • Recombinant factor VIIa (Novoseven®) can be repeated in 2 to 4 hours if severe bleeding continues.

IV = Intravenous

Reversal of warfarin for invasive or surgical procedures

14. It is recommended to hold warfarin in patients undergoing invasive or surgical procedures as indicated in Table 4 (*Local Consensus [5], Douketis 2008 [5a]*).

Table 4: Managing anticoagulation in patients requiring invasive or surgical procedures (*Local Consensus [5], Douketis 2008 [5a]*)

Condition	Description
Low risk* of thromboembolism	<ul style="list-style-type: none"> • Stop warfarin therapy 4 to 5 days before surgery. • Allow the INR to return to near normal. • Briefly use postoperative prophylaxis (if the intervention itself creates a higher risk of thrombosis) with a prophylactic dose of LMWH and simultaneously begin warfarin therapy. • Alternatively, a low dose of UFH or a prophylactic dose of LMWH can also be used preoperatively. • No reversal of warfarin is necessary for most surgeries if the INR is ≤ 1.5.
Intermediate risk of thromboembolism	<ul style="list-style-type: none"> • Stop warfarin 4 to 5 days before surgery. • Allow the INR to fall. • Cover the patient beginning 2 days preoperatively with a prophylactic dose of LMWH. • Restart therapy with LMWH and warfarin post-operatively. • Alternatively, administer a full dose of LMWH post-operatively.
High risk# of thromboembolism	<ul style="list-style-type: none"> • Stop warfarin 4 to 5 days before surgery. • Allow the INR to return to normal. • Begin therapy with a full dose of UFH or a full dose of LMWH as the INR falls (approximately 2 days preoperatively). • Discontinue UFH approximately 5 hours prior to surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery. • Alternatively, continue with LMWH and stop therapy 12 to 24 hours prior to surgery with the expectation that the anticoagulant effect will have worn off at the time of surgery.
Low risk of bleeding	<ul style="list-style-type: none"> • Continue warfarin therapy at a lower dose. • Operate at an INR of 1.3 to 1.5. • The dose of warfarin can be lowered 4 to 5 days before surgery. • Warfarin therapy can be restarted post-operatively. • May be supplemented with a prophylactic dose of LMWH.

*Low risk of thromboembolism includes no recent (> 3 months) venous thromboembolism, atrial fibrillation without a history of stroke or other risk factors, or bileaflet mechanical cardiac valve in aortic position.

#High risk of thromboembolism includes recent (3 months) history of venous thromboembolism, mechanical cardiac valve in mitral position, or old model of cardiac valve (ball/cage).

15. It is recommended, for patients undergoing dental extractions, consider use of tranxemic mouthwash or epsilon aminocaproic acid mouthwash without interruption of anticoagulation therapy (*Local Consensus [5]*).

Transitioning Warfarin Therapy

16. It is recommended to transition warfarin to and from other anticoagulant medications as described in Table 5 (*Local Consensus [5], Ansell 2008 [5a], Monagle 2008 [5a]*).

Table 5: Transitioning warfarin to or from another anticoagulant medication (*Local Consensus [5], Ansell 2008 [5a], Monagle 2008 [5a]*)

Transitioning Medications (Current to New)	Stop Current Medication	Start New Medication
Warfarin to LMWH	Stop warfarin when clinically indicated or 5 days prior to procedure	Start LMWH on the third day of holding warfarin*
Warfarin to UFH	Stop warfarin when clinically indicated or 5 days prior to procedure	Start UFH on the third day of holding warfarin
LMWH to Warfarin	Stop LMWH after a minimum of 5 days or after two consecutive therapeutic INRs	Start warfarin when clinically indicated and patient able to tolerate medication
UFH to Warfarin	Stop UFH after a minimum of 5 days or when warfarin INR is therapeutic	Start warfarin when clinically indicated and patient able to tolerate medication

*Patients with a higher clotting risk may be started on LMWH immediately upon the discontinuation of warfarin (*Local Consensus [5]*).
LMWH = Low Molecular Weight Heparin; UFH = Unfractionated heparin

Discontinuation of warfarin therapy in pregnancy

17. It is recommended to immediately discontinue warfarin therapy if a patient suspects she may be pregnant (Bates 2008 [5a]).

Note: Warfarin exposure in the first trimester of pregnancy may be associated with warfarin embryopathy (Bates 2008 [5a]).

Duration of Therapy

18. It is recommended to refer patient to a specialist for the ongoing outpatient management of warfarin therapy (Monagle 2008 [5a]).

Note 1: Duration of warfarin therapy is dependent on indication (Monagle 2008 [5a]).

Note 2: CCHMC sponsors a Thrombophilia Program that manages patients receiving warfarin (Phone: 513-636-6213) (Local Consensus [5]).

Education

19. It is recommended to instruct the patient/parent to inform the clinician of any changes or additions in medication or diet (Monagle 2008 [5a]).

Note 1: Warfarin is metabolized via cytochrome P450 2C9 substrate and is associated with many drug-drug interactions (Ansell 2008 [5a]).

Note 2: CCHMC has warfarin patient educational material through Knowing Notes and Health Topics.

- [Vitamin K and Wafarin - Your child's diet](#), [Vitamin K Warfarin - Spanish Version](#)
- [Warfarin \(Coumadin\) Brochure](#), [Warfarin - Spanish Version](#)
- Health Topic: **Warfarin**

20. It is recommended to instruct the patient/parent to inform other healthcare providers involved in the patient's care about being on anticoagulant therapy (Monagle 2008 [5a]).

21. It is recommended that patients receiving warfarin therapy use a "Medical Alert" bracelet or pendant (Ansell 2008 [5a]).

Discussion/summary of evidence

Based upon an AGREE evaluation of the *Chest* American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), we concluded that the working group published a well-developed guideline (Ansell 2008 [5a]). The Applicability domain scored relatively low. This score takes into account discussions in the guideline of how to apply the recommendations to practice. While the guidelines do not specifically address how to apply them to clinical practice, all the recommendations are clearly identified, and the review team did not feel this decreased the validity of the guidelines.

Standardized AGREE domain scores:

Scope and Purpose	96%
Stakeholder Involvement	53%
Rigor of Development	95%
Clarity and Presentation	72%
Applicability	30%
Editorial Independence	94%

(Crary 2008 [4b], Local Consensus [5], Ansell 2008 [5a], Bates 2008 [5a], Douketis 2008 [5a], Guyatt 2008 [5a], Hirsh 2008a [5a], Hirsh 2008b [5a], Kearon 2008 [5a], Monagle 2008 [5a])

Health Benefits, Side Effects and Risks


Health Benefits: Following these recommendations when managing patients on warfarin therapy may help to minimize both over-coagulation (thrombus formation) and under-coagulation (bleeding) in these patients (Ansell 2008 [5a]).

Side Effects: Bleeding is the main complication of warfarin therapy. Nonhemorrhagic complications, such as tracheal calcification or hair loss, have been described on rare occasions in young children. Reduced bone density in children

receiving warfarin for more than one year has been reported (*Monagle 2008 [5a]*). Other than bleeding, the most important side effect of warfarin is skin necrosis. This uncommon complication is usually observed on the third to eighth day of therapy and is caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat (*Ansell 2008 [5a]*). An association between warfarin-induced skin necrosis and protein C deficiency and, less commonly, protein S deficiency has been reported (*Ansell 2008 [5a]*).

Risks: The most important factor influencing the risk of bleeding is the intensity of anticoagulation therapy as observed by higher INRs (*Ansell 2008 [5a]*).

References

Note: When using the electronic version of this document,  indicates a hyperlink to the PubMed abstract. A hyperlink following this symbol goes to the article PDF when the user is within the CCHMC network.

1. **Ansell, J.; Hirsh, J.; Hylek, E.; Jacobson, A.; Crowther, M.; and Palareti, G.:** Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 160S-198S, 2008, [5a] [_____ !\[\]\(9bf097d682561b2ffd12d57a40ca73b1_img.jpg\) _____](#).
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4. **Douketis, J. D.; Berger, P. B.; Dunn, A. S.; Jaffer, A. K.; Spyropoulos, A. C.; Becker, R. C.; and Ansell, J.:** The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 299S-339S, 2008, [5a] [_____ !\[\]\(5ec38675172d195694038a5f80a05d7e_img.jpg\) _____](#).
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8. **Kearon, C.; Kahn, S. R.; Agnelli, G.; Goldhaber, S.; Raskob, G. E.; and Comerota, A. J.:** Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 454S-545S, 2008, [5a] [_____ !\[\]\(b0b63490044f422217aa04e636af653e_img.jpg\) _____](#).
9. **Local Consensus:** During BEST development timeframe. [5].
10. **Monagle, P.; Chalmers, E.; Chan, A.; DeVeber, G.; Kirkham, F.; Massicotte, P.; and Michelson, A. D.:** Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*, 133(6 Suppl): 887S-968S, 2008, [5a] [_____ !\[\]\(7ccfdf327d906fe450820dbe51161eb8_img.jpg\) _____](#).

Note: Full tables of evidence grading system available in separate document:

- [Table of Evidence Levels of Individual Studies by Domain, Study Design, & Quality](#) (abbreviated table below)
- [Grading a Body of Evidence to Answer a Clinical Question](#)
- [Judging the Strength of a Recommendation](#) (abbreviated table below)

Table of Evidence Levels (see note above)

<i>Quality level</i>	<i>Definition</i>
1a† or 1b†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5	Other: General review, expert opinion, case report, consensus report, or guideline

†a = good quality study; b = lesser quality study

Table of Recommendation Strength (see note above)

<i>Strength</i>	<i>Definition</i>
“Strongly recommended”	There is consensus that benefits clearly outweigh risks and burdens (or visa-versa for negative recommendations).
“Recommended”	There is consensus that benefits are closely balanced with risks and burdens.
No recommendation made	There is lack of consensus to direct development of a recommendation.

Dimensions: In determining the strength of a recommendation, the development group makes a considered judgment in a consensus process that incorporates critically appraised evidence, clinical experience, and other dimensions as listed below.

1. Grade of the Body of Evidence (see note above)
2. Safety / Harm
3. Health benefit to patient (*direct benefit*)
4. Burden to patient of adherence to recommendation (*cost, hassle, discomfort, pain, motivation, ability to adhere, time*)
5. Cost-effectiveness to healthcare system (*balance of cost / savings of resources, staff time, and supplies based on published studies or onsite analysis*)
6. Directness (*the extent to which the body of evidence directly answers the clinical question [population/problem, intervention, comparison, outcome]*)
7. Impact on morbidity/mortality or quality of life

Supporting information

Introductory/background information

Warfarin is a vitamin K antagonist and functions as an anticoagulant by reducing the plasma levels of functional vitamin-K dependent coagulation factors (factors II, VII, IX and X) and the vitamin-K dependent anticoagulation factors protein C and S (*Ansell 2008 [5a]*).

Half-Life: Warfarin has a serum half-life of 36 to 42 hours and accumulates in the liver (*Ansell 2008 [5a]*).

Genetic Factors: Cytochrome P450 2C9 is the enzyme responsible for warfarin metabolism; a common mutation of the gene responsible for this enzyme causes reduced warfarin requirements. A mutation of the warfarin receptor is responsible for warfarin resistance in which higher plasma warfarin levels are required to achieve therapeutic anticoagulation. A mutation of the factor IX polypeptide may cause selective reduction in factor IX during treatment with warfarin and may be associated with increased bleeding at the usual therapeutic INR (*Ansell 2008 [5a]*).

Drugs and diet: Drugs, diet and various disease states can alter the pharmacokinetics of warfarin. Common drug interactions include: trimethoprim-sulfamethoxazole (inhibits warfarin metabolism), Cimetidine and omeprazole (moderately inhibit the metabolism of warfarin), barbiturates and rifampin (inhibit the anticoagulant effect of warfarin by increasing hepatic clearance), second and third generation cephalosporins (increase the anticoagulant effect of

warfarin by interfering with the P450 enzymes). Over-the-counter herbal medicines may also affect warfarin metabolism (Ansell 2008 [5a]).

Group/team members

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Search strategy

CHEST 2008 Anticoagulation Guidelines.

In addition, a search was conducted for literature published subsequent to the Chest Guidelines:

OID MEDLINE; search terms:anticoagu\$ (explode), Warfarin, Child, Treat\$ or Thera\$,
with limits and filters: English language, Humans, Age Range 0-18 years.

Known conflicts of interest

Conflicts of interest were declared and none were found.

Applicability Issues

Outcome measure: If a baseline INR was obtained no more than seven days prior to the first dose of warfarin in the hospital. The quality of management of anticoagulant therapy can be measured by determining time in therapeutic range. This is expressed as the fraction of INR values that are within therapeutic range (e.g., the number of INRs in the range divided by the number of INR tests).

Copies of this Best Evidence Statement (BESt) are available online and may be distributed by any organization for the global purpose of improving child health outcomes. Website address: <http://www.cincinnatichildrens.org/svc/alpha/h/health-policy/ev-based/default.htm>

Examples of approved uses of the BESt include the following:

- copies may be provided to anyone involved in the organization's process for developing and implementing evidence based care;
- hyperlinks to the CCHMC website may be placed on the organization's website;
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- copies may be provided to patients and the clinicians who manage their care.

Notification of CCHMC at HPCEInfo@cchmc.org for any BESt adopted, adapted, implemented or hyperlinked by the organization is appreciated.

For more information about this CCHMC Best Evidence Statement and the development process, contact Cynthia Barclay, Pharm.D in the Division of Pharmacy at: 513-636-4292 or cynthia.barclay@cchmc.org.

Note

This Best Evidence Statement addresses only key points of care for the target population; it is not intended to be a comprehensive practice guideline. These recommendations result from review of literature and practices current at the time of their formulation. This Best Evidence Statement does not preclude using care modalities proven efficacious in studies published subsequent to the current revision of this document. This document is not intended to impose standards of care preventing selective variances from the recommendations to meet the specific and unique requirements of individual patients. Adherence to this Statement is voluntary. The clinician in light of the individual circumstances presented by the patient must make the ultimate judgment regarding the priority of any specific procedure.

Reviewed by Clinical Effectiveness and Center for Professional Excellence.