The information contained in this ICSI Health Care Guideline is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. If you are not one of the expert audiences listed above you are urged to consult a health care professional regarding your own situation and any specific medical questions you may have. In addition, you should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in your individual case.

This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician’s judgment or to establish a protocol for all patients with a particular condition. An ICSI Health Care Guideline rarely will establish the only approach to a problem.

Copies of this ICSI Health Care Guideline may be distributed by any organization to the organization’s employees but, except as provided below, may not be distributed outside of the organization without the prior written consent of the Institute for Clinical Systems Improvement, Inc. If the organization is a legally constituted medical group, the ICSI Health Care Guideline may be used by the medical group in any of the following ways:

- copies may be provided to anyone involved in the medical group’s process for developing and implementing clinical guidelines;
- the ICSI Health Care Guideline may be adopted or adapted for use within the medical group only, provided that ICSI receives appropriate attribution on all written or electronic documents; and
- copies may be provided to patients and the clinicians who manage their care, if the ICSI Health Care Guideline is incorporated into the medical group’s clinical guideline program.

All other copyright rights in this ICSI Health Care Guideline are reserved by the Institute for Clinical Systems Improvement. The Institute for Clinical Systems Improvement assumes no liability for any adaptations or revisions or modifications made to this ICSI Health Care Guideline.
### INDEX OF ANNOTATIONS AND DISCUSSION/REFERENCES

<table>
<thead>
<tr>
<th>Topic</th>
<th>Annotation</th>
<th>Page Number</th>
<th>Letter “D” indicates accompanying discussion and references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WARFARIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
<td>5</td>
<td>D</td>
</tr>
<tr>
<td>Indications</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>3</td>
<td>5-6</td>
<td>D</td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>4</td>
<td>6-7</td>
<td>D</td>
</tr>
<tr>
<td>Dosing</td>
<td>5</td>
<td>7-9</td>
<td>D</td>
</tr>
<tr>
<td>Monitoring</td>
<td>6</td>
<td>9-11</td>
<td>D</td>
</tr>
<tr>
<td>Correction of Supratherapeutic Anticoagulation Caused by Warfarin</td>
<td>7</td>
<td>11-12</td>
<td>D</td>
</tr>
<tr>
<td><strong>HEPARIN (UNFRACTIONATED AND LOW-MOLECULAR-WEIGHT HEPARIN) AND SYNTHETIC PENTASACCHARIDE (FONDAPARINUX)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>8</td>
<td>12-13</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Precautions</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>12</td>
<td>13-14</td>
<td>D</td>
</tr>
<tr>
<td><strong>UNFRACTIONATED HEPARIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>13</td>
<td>15</td>
<td>D</td>
</tr>
<tr>
<td>Monitoring</td>
<td>14</td>
<td>15-16</td>
<td>D</td>
</tr>
<tr>
<td>Correction of Supratherapeutic Anticoagulation Caused by UFH</td>
<td>15</td>
<td>16</td>
<td>D</td>
</tr>
<tr>
<td><strong>LOW-MOLECULAR-WEIGHT HEPARIN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>16</td>
<td>16-17</td>
<td>D</td>
</tr>
<tr>
<td>Monitoring</td>
<td>17</td>
<td>18</td>
<td>D</td>
</tr>
<tr>
<td>Correction of Supratherapeutic Anticoagulation Caused by LMWH</td>
<td>18</td>
<td>19</td>
<td>D</td>
</tr>
<tr>
<td>Precautions</td>
<td>19</td>
<td>19-20</td>
<td>D</td>
</tr>
<tr>
<td>Bridging Therapy</td>
<td>20</td>
<td>20-21</td>
<td>D</td>
</tr>
<tr>
<td><strong>SYNTHETIC PENTASACCHARIDE (FONDAPARINUX)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>21</td>
<td>21-22</td>
<td>D</td>
</tr>
<tr>
<td>Monitoring</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>
# Table of Contents

<table>
<thead>
<tr>
<th>Overview</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Scope and Target Population</td>
<td>3</td>
</tr>
<tr>
<td>Related ICSI Scientific Documents</td>
<td>3</td>
</tr>
<tr>
<td>Clinical Highlights for Individual Clinicians</td>
<td>3-4</td>
</tr>
<tr>
<td><em>(Recommendations for application in individual clinician practice)</em></td>
<td></td>
</tr>
<tr>
<td>Brief Description of Evidence Grading</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Annotations</th>
<th>5-33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix A – Risk Factors for Bleeding During Warfarin Therapy</td>
<td>23</td>
</tr>
<tr>
<td>Appendix B – Recommended Therapeutic Range for Oral Anticoagulant Therapy</td>
<td>24</td>
</tr>
<tr>
<td>Appendix C – Drug/Herbal Interactions with Warfarin</td>
<td>25-27</td>
</tr>
<tr>
<td>Appendix D – Endogenous Interactions with Warfarin</td>
<td>28</td>
</tr>
<tr>
<td>Appendix E – Patient Education Guide to Warfarin Therapy</td>
<td>29-30</td>
</tr>
<tr>
<td>Appendix F – Example of a Heparin Nomogram</td>
<td>31</td>
</tr>
<tr>
<td>Appendix G – Direct Thrombin Inhibitors</td>
<td>32</td>
</tr>
<tr>
<td>Appendix H – Glossary of Abbreviations</td>
<td>33</td>
</tr>
</tbody>
</table>

| Discussion & References *(Discussion with Reference Citations)*         | 34-51|
| Disclosure of Potential Conflict of Interest                            | 35   |
| Full Description of Evidence Grading                                    | 36   |
| Discussion with Reference Citations                                     | 37-51|

| Support for Implementation *(Implementation measures, strategies and materials)* | 52-54 |
| Recommended Internet Websites for Providers and/or Patients             | 53-54 |
**Overview**

**INTRODUCTION**

The ICSI Anticoagulation Therapy Supplement has been developed as a resource for the use of anticoagulant drugs. This is a supplemental document that brings about consistency in recommendations that are common to the scope of related ICSI guidelines: Atrial Fibrillation, Congestive Heart Failure, Inpatient Management of Heart Failure, Diagnosis and Initial Treatment of Ischemic Stroke, Treatment of Acute Myocardial Infarction, Venous Thromboembolism, and Venous Thromboembolism Prophylaxis for Surgical/Trauma Patients.

Anticoagulant drugs are used to decrease the risk of thrombosis by interfering with the homeostatic clotting mechanism. The major side effect of these drugs is bleeding either from supratherapeutic effect or by accentuating the blood loss of patients with an existing source of bleeding.

There are no absolute contraindications to anticoagulation therapy. The decision to treat a patient with anticoagulant drugs takes into account an individual patient’s risk for thrombosis if not treated weighed against the risk of bleeding while on anticoagulation therapy. This supplement and related guidelines should help physicians to make that risk-benefit treatment decision. This supplement is also meant to serve as a tool to use for patients treated with anticoagulants.

A glossary of abbreviations used throughout this guideline is attached in Appendix H, "Glossary of Abbreviations."

**SCOPE AND TARGET POPULATION**

This guideline supplement is targeted for any patient receiving anticoagulation therapy. Please refer to related guidelines for specific target populations.

**RELATED ICSI SCIENTIFIC DOCUMENTS**

This document is a supplement to the following ICSI guidelines which make recommendations for anticoagulation therapy:

1. Atrial Fibrillation
2. Congestive Heart Failure
3. Inpatient Management of Heart Failure
4. Diagnosis and Initial Treatment of Ischemic Stroke
5. Treatment of Acute Myocardial Infarction
6. Venous Thromboembolism
7. Venous Thromboembolism Prophylaxis for Surgical/Trauma Patients

**CLINICAL HIGHLIGHTS FOR INDIVIDUAL CLINICIANS**

1. There are no circumstances under which patients absolutely should or should not receive anticoagulation therapy. Clinicians must consider the risks and benefits of anticoagulation therapy for a patient based upon the individual’s risk for thrombosis if not treated weighed against the risk of bleeding if treated. (*Introduction, Annotations #2, 3, 4, 9, 10, 11, 12*)
2. In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate-acting anticoagulant agents (UFH/LMWH) should be used concomitantly with warfarin. (Annotation #5)

3. Loading doses and rapid induction of warfarin (Coumadin®) should be avoided. (Annotation #5)

4. Vitamin K may be used to reverse supratherapeutic anticoagulation with warfarin. The dose of vitamin K depends upon the degree of INR elevation and/or signs and symptoms of bleeding (Table 2). Vitamin K can lead to warfarin resistance and subsequently to an increased risk of thromboembolism. (Annotation #7)

5. Any prescription medication or over-the-counter remedy, including herbs, may alter the effectiveness of anticoagulants. (Annotations #5, 23, Annotation Appendices C, D, E)

6. Regardless of the anticoagulant used, it is important that patients know they must always inform their physician and other health care providers that they are on anticoagulation therapy, especially if they are potentially undergoing an invasive procedure. (Annotations #6, 17, Appendix E)

7. Patients should be encouraged and empowered to play an active role in the self-management of their treatment. Self-management is best initiated and sustained through active involvement of patients and family members with their multidisciplinary health care team. This educational partnership should be encouraged to decrease potential risks and improve understanding of the importance of patient adherence to their treatment regimen. (Annotations #6, 17, Appendix E)

**Evidence Grading**

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

A full explanation of these designators is found in the Discussion and References section of the guideline.
WARFARIN

1. Introduction
Warfarin is used in the chronic management of patients with several types of thrombotic diseases. It produces its anticoagulant effect by inhibiting the vitamin K dependent production of clotting factors II, VII, IX, X, and proteins C and S. Warfarin is not fully effective in the initial several days of therapy because of a delayed reduction in some of the clotting factors that it inhibits. In the initial phase of treatment for patients with active thrombosis (such as acute deep vein thrombosis [DVT]) or high risk of thrombosis, immediate-acting anticoagulant agents (UFH, LMWH) should be used concomitantly with warfarin.

2. Indications
Indications for use of warfarin are outlined in ICSI guidelines related to this supplement.

3. Contraindications
All contraindications are relative to a patient’s risk for thrombosis weighed against the risk for bleeding while on anticoagulation therapy.

A. Warfarin Allergy or Intolerance
Acute rash, hepatitis, diarrhea, or nausea may indicate an allergy or intolerance to warfarin.

B. Hemorrhage
Anticoagulation with warfarin is contraindicated in patients with active hemorrhage with possible exceptions in certain circumstances such as disseminated intravascular coagulation as a result of malignancy. The decision to initiate anticoagulation should be individualized for patients with a history of recent hemorrhage. Again, this is dependent on circumstances including the type of hemorrhage and the indication for anticoagulation. Withholding anticoagulation for 4-6 weeks may be prudent for non-central nervous system bleeds. This duration may be longer for central nervous system (CNS) bleeds and needs to be assessed on a case-by-case basis.

C. Pregnancy
Warfarin is contraindicated during pregnancy because it crosses the placenta causing teratogenicity and fetal bleeding. Unfractionated and low-molecular-weight heparins do not cross the placenta and do not cause teratogenicity or fetal bleeding. Therefore, unfractionated heparin (UFH) or a low-molecular-weight heparin (LMWH) should be used in place of warfarin. A recent study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert.

The amount of warfarin in breast milk is too small to affect the baby. As a result, breast-feeding is safe for mothers taking warfarin and for their infants.

Evidence supporting this recommendation is of class: R
D. Exclusion Criteria

Table 1: Exclusion Criteria Used in Trials Evaluating the Efficacy and Tolerability of Anticoagulation in Patients with Nonvalvular Atrial Fibrillation

Note: The potential increased risk of bleeding must be balanced against the potential decreased risk of thromboembolism.

- Active bleeding
- Active peptic ulcer disease
- Known coagulation defects
- Thrombocytopenia (platelets < 50,000/mm$^3$) or platelet dysfunction
- Recent hemorrhagic stroke
- Noncompliant or unreliable patients
- Patient is psychologically or socially unsuitable
- Dementia or severe cognitive impairment
- History of falls (3 within the previous year or recurrent, injurious falls)
- Excessive alcohol intake
- Uncontrolled hypertension (> 180/100 mm Hg)
- Daily use of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Planned invasive procedure or major surgery


Please refer to Annotation Appendix A, "Risk Factors for Bleeding During Warfarin Therapy" and the Discussion Section for additional information about predicting the risk of bleeding for individual patients.

4. Adverse Effects

A. Bleeding

The most common adverse effect of warfarin is bleeding. Risk factors for bleeding should not be considered absolute contraindications to anticoagulant therapy. Some risk factors for bleeding (such as age) are also risk factors for thromboembolism. **The potential increased risk of bleeding must be balanced against the potential decreased risk of thromboembolism.** Risk of bleeding is reduced by using lower intensity of anticoagulation and by avoiding concomitant use of aspirin. Please refer to Annotation Appendix A, "Risk Factors for Bleeding During Warfarin Therapy" and the Discussion Section for additional information on bleeding risk in anticoagulation therapy.

B. Skin Necrosis

Skin necrosis is a rare but serious complication of warfarin therapy that typically occurs on the third to eighth day of therapy. Warfarin should be discontinued in patients with evidence of skin necrosis.
necrosis. These patients should be placed on heparin unless there is evidence of heparin induced thrombocytopenia (HIT).

C. **Purple Toe Syndrome**

Purple toe syndrome and other manifestations of peripheral emboli may rarely complicate warfarin therapy, usually 3-10 weeks after initiation of therapy. Causes of purple toe syndrome other than warfarin should be considered when making a treatment decision. These include vasculitis, acute myocardial infarction (MI) with embolism, and diabetes mellitus.

D. **Less Serious Adverse Effects**

Adverse effects that are less serious include alopecia, osteoporosis, gastrointestinal discomfort and rash. Management of these adverse effects should be managed on an individual basis.

**Evidence supporting this recommendation is of classes: B, D, R**

5. **Dosing**

A. **General Principles of Warfarin Dosing**

1. Loading doses for rapid induction of warfarin should be avoided. Warfarin (irrespective of INR) is not fully effective in the first several days of therapy because of a delayed decrease in several circulating clotting factors. Loading doses can increase a patient’s risk of supra-therapeutic INR and make it more difficult to determine a steady-state dose.

2. Patients at high risk for thrombosis, such as those with an active thrombotic process (e.g. VTE) or an underlying malignancy, should be treated with concomitant heparin and warfarin therapy. Patients at lower thrombotic risk (e.g. atrial fibrillation without recurrent thromboembolism) can be initiated on warfarin alone.

3. A single target INR value should be used as a goal endpoint. This will decrease the odds of a patient being above or below a desirable range of INR. The target INR for most conditions is 2.5 with an acceptable range of 2.0-3.0. Other thrombotic conditions (e.g. mitral mechanical valves) have recommended targets of 3.0 (range 2.5-3.5). A table of recommended therapeutic ranges for oral anticoagulant therapy is attached in Annotation Appendix B. Also, individual disease management guidelines such as Atrial Fibrillation and VTE give specific INR recommendations.

4. The risk of bleeding for patients on warfarin increases substantially at INR values greater than 4.0. This risk is magnified if one or more risk factors are present. Consider hemorrhagic risk in all dosing decisions. Please refer to Annotation Appendix A, "Risk Factors for Bleeding During Warfarin Therapy," for more information on risk factors for bleeding during warfarin therapy.

5. There is a significant increase in thromboembolism as INR values decrease below INR 1.7. Clinical risk and past medical history should be considered in all dosing decisions. Higher risk may require more aggressive dosing.

6. In most cases, holding warfarin for 4 days prior to surgery results in an INR value of 1.2 or less. Expect advanced age and drug interactions to result in a slower decline. Patients with high risk of thromboembolism may need coverage with heparin for a portion of this time. For more information, please refer to Annotation #20, "Bridging Therapy."
7. Some equivalency studies have shown that substitution of generic warfarin for brand name Coumadin® may provide equivalent anticoagulation response if the manufacturer of the generic warfarin has followed the standards set for the name brand. Care must be taken to remain with either the brand name product or the same generic product. Do not switch from brand to generic or between generics.

8. Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Herbal or natural remedies can change the INR response to warfarin and/or increase a patient’s risk of bleeding. In these instances, additional monitoring may be needed. Please refer to Annotation Appendices C, "Drug/Herbal Interactions with Warfarin," and D, "Endogenous Interactions with Warfarin" for more information.

9. Foods that contain moderate amounts of vitamin K may decrease the INR response to warfarin. Please refer to Annotation Appendix E, "Patient Education Guide to Warfarin Therapy" for a guide to educating patients regarding warfarin therapy.

10. Direct thrombin inhibitors (hirudin, argatroban, bivalirudin) and heparins can affect the INR. Please refer to Annotation Appendix G, "Direct Thrombin Inhibitors" for more information.

Evidence supporting this recommendation is of classes: A, B, D, R

B. Initiation of Warfarin

1. **Average Daily Dosing Technique (for patients not on heparin)**
   a. Patients receiving warfarin for the first time should begin at an average dose of 5mg daily with a recheck of INR in 2-3 doses. Moderate initiation doses should be considered for patients with any of the following factors: age greater than 75 years, multiple comorbid conditions, poor nutrition (low albumin), elevated INR when off warfarin, elevated liver function tests, or changing thyroid status. Average daily dosing technique is useful for patients off UFH and LMWH. Higher initial dosing nomograms have not shown consistent benefit.
   b. Therapy for patients previously taking warfarin can be initiated at the previous dose.
   c. A baseline INR value may be drawn to rule out underlying coagulopathy.
   d. If the INR is 2.0 or greater after the first 3 doses, consider decreasing the dose by one-half. Always search for causes of rapid rise in INR.
   e. Subsequent INR values are determined at 2-3 times weekly for 1-2 weeks, then less often depending on the stability of the INR result.
   f. Steady state anticoagulation occurs between 6 to 12 days. Expect obese patients and patients of advanced age to have a longer time to steady state.

Evidence supporting this recommendation is of class: A

2. **Flexible Daily Dosing Technique (for patients on heparin)**
   a. Patients are given daily doses of warfarin, adjusted according to the daily INR, until a weekly dose can be determined. The flexible daily dosing technique is useful for patients on concomitant UFH or a LMWH.
b. The dose-response relationship is best interpreted when there are at least 16 hours between dose and laboratory draw.

c. For patients who weigh more than 80 kg, a higher estimated average initial dose of 7.5 mg may be given.

Evidence supporting this recommendation is of class: D

C. Maintenance Dosing of Warfarin

Numerous factors should be considered with regard to warfarin dosing including diagnosis, sensitivity to warfarin, age (especially if elderly), patient adherence, other medications (e.g. amiodarone), body mass, alcohol consumption, nutritional status, diet/dietary changes, activity level, race, and accuracy of laboratory results.

1. Dose adjustments should be made in increments of up to 15% of the weekly dose.

2. An assessment of clinical variables known to affect the INR should be made with each dose adjustment. Always search for the cause of out-of-range values and address them before adjusting the dose.

3. Expect a 15% dose adjustment to result in an approximately 1.0 INR change. Likewise, a 10% dose adjustment will result in an approximate 0.7-0.8 INR change.

4. Steady-state INR values will not be realized for up to 3 weeks following a dose adjustment.

5. Patients with INR values by ± 0.5 INR out-of-range should be considered for more frequent monitoring and should have a repeat INR within seven days.

6. If two consecutive weekly INR values are within range and there has not been a change in warfarin variables, increase the interval between draws to 2 weeks.

6. Monitoring

A. Principles of Monitoring Warfarin Therapy

1. The dose-response relationship is best interpreted when at least 16 hours elapse between dose and lab draw.

2. Plasma for INR testing should be anticoagulated using 3.2% citrate.

3. INR determinations should be obtained monthly in most stable patients, but not more than 6 weeks should elapse between determinations.

4. Heparin and lupus anticoagulants may spuriously prolong INR results obtained by some instrument-reagent combinations.

Evidence supporting this recommendation is of classes: B, D, R

B. Options for Monitoring and Management

1. Over the past decade, options for monitoring and managing warfarin have emerged. With the improvement of point-of-care instruments, the INR can now be measured in the office (office point-of-care monitoring) or at home by the patient (self-monitoring) as well as in the laboratory.
Algorithm Annotations (cont)

Anticoagulation Therapy Supplement

a. Point-of-care coagulation instruments using whole blood or plasma specimens can be utilized for INR testing. Accuracy and precision data should be evaluated when selecting one of these instruments.

b. INRs obtained simultaneously on the same blood sample using point-of-care and laboratory instruments will not be identical due to differences in reagents, testing methods and specimen type.

c. Accuracy of a point-of-care instrument can diminish over time due to changes in reagents, aging of the detection system, and poor maintenance. Periodic accuracy checks with the laboratory coagulation analyzer are indicated.

d. Each point-of-care instrument should be evaluated to determine the range of accurate INR results (reportable range). INR results outside this range should be confirmed in the laboratory.

2. Traditionally, warfarin has been monitored and managed by the patient’s personal physician. However, much like diabetes, new management options have emerged including anticoagulation clinics staffed by pharmacists and/or RNs, and patient-directed management (self-management). These anticoagulation programs have been shown to significantly reduce patients’ risks of adverse outcomes.

Please refer to Discussion #6, B2 for resources on development and support of anticoagulation clinics.

Evidence supporting this recommendation is of classes: B, C, D, R

C. Key Patient Education Components: Warfarin


2. Time of day to take warfarin: it should be taken at approximately the same time and is taken in the evening. Due to the short half-life of factor VII and its influence on the INR, this is especially important if the patient will have an INR drawn the next morning.

3. Explanation of INR, target range and regular testing.

4. Signs and symptoms of bleeding and that the provider should be contacted immediately if bleeding signs are present.

5. Need to notify provider if illness, injury or change in physical status occurs.

6. Need to inform all their health care providers that they are on anticoagulation therapy, especially if they are potentially undergoing an invasive procedure, surgery or dental work.

7. Drug interactions:
   • What to do if a new medication is initiated or a medication is discontinued, especially if the interaction with warfarin in unknown: check INR within 3-4 days.
   • Drugs that affect the absorption of warfarin.
   • Drugs that increase or decrease the effect of warfarin.
Algorithm Annotations (cont)

- Common over-the-counter medication interactions including aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, natural or herbal remedies, laxatives, antacids, and multivitamin preparations containing vitamin K.

8. Role of vitamin K and the importance of consistency of vitamin K rich foods in the diet rather than avoidance of vitamin K rich foods.

9. Importance of minimizing trauma risk associated with activities at high risk for injury.

10. Effect of exercise: increased activity results in decreased effect of the drug.

11. Effect of personal habits: alcohol, chewing tobacco, etc.

12. Effect of certain conditions: congestive heart failure, thyroid disease, gastroenteritis and diarrhea.

13. Importance of self-monitoring: maintain a log of INRs, dose of warfarin, etc.

14. Medic Alert bracelet/necklace and warfarin ID card.

Please refer to Annotation Appendix E, ”Patient Education Guide to Warfarin Therapy” for a guide to patient education regarding warfarin therapy.

7. Correction of Supratherapeutic Anticoagulation Caused by Warfarin

Supratherapeutic anticoagulation may occur with patients taking warfarin. Vitamin K may be used to reverse the effects of warfarin, however, vitamin K can lead to warfarin resistance and subsequently, to an increased risk of thromboembolism.

**Important Considerations for Vitamin K Dosing**

1. In an outpatient clinic setting, oral vitamin K is the preferred route of administration.

2. In a hospital setting, when patients are NPO or ill, intravenous vitamin K may be the preferred route of administration. To avoid anaphylactic reactions, vitamin K should be given over 30 minutes in a mixture of D5W 50 mL under monitored conditions. It is not necessary to premedicate with corticosteroids or antihistamines.

3. Administration of subcutaneous vitamin K can lead to erratic correction of the INR and unpredictable resistance to warfarin.

4. Intramuscular injections of vitamin K should be avoided.
Table 2: Correction of Supratherapeutic Warfarin Anticoagulation caused by Warfarin

<table>
<thead>
<tr>
<th>Bleeding Severity</th>
<th>INR</th>
<th>Vitamin K</th>
<th>FFP  (15cc/kg rounded to the nearest unit)</th>
<th>Warfarin</th>
<th>Next INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Serious</td>
<td>&lt; 5</td>
<td>none</td>
<td>none</td>
<td>omit/adjust dose</td>
<td></td>
</tr>
<tr>
<td>Bleeding and</td>
<td>5.0-8.9</td>
<td>0, 1, or 2.5 mg PO</td>
<td>none</td>
<td>omit/adjust dose</td>
<td>next day</td>
</tr>
<tr>
<td>Without Urgent/</td>
<td></td>
<td>3-5 mg PO</td>
<td>none</td>
<td>omit/adjust dose</td>
<td>6-24 hours</td>
</tr>
<tr>
<td>Recent Surgery</td>
<td>9.0-20.0</td>
<td></td>
<td>none</td>
<td>omit/adjust dose</td>
<td>immediately following FFP, with re-check 12-24 hours later</td>
</tr>
<tr>
<td>&gt; 20.0*</td>
<td></td>
<td>10 mg slow IV infusion</td>
<td>FFP*</td>
<td>omit/adjust dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>may be repeated q 12 hr</td>
<td></td>
<td>immediately following FFP, with re-check 12-24 hours later</td>
<td></td>
</tr>
</tbody>
</table>

| Serious Bleeding  | Up to 8.9| 2.5 mg PO               | FFP*                                       | omit              | 6-24 hours                   |
|                   | 9.0-20   | 5 mg PO                 | FFP*                                       | omit              | 6-24 hours                   |
|                   | > 20     | 10 mg slow IV infusion  | FFP*                                       | omit              | 6-24 hours                   |
|                   |          | NO SUB Q.               |                              |                   |                              |

Key: FFP = fresh frozen plasma
Vit K, available as 5 mg tab, IV solution
* Vitamin K and FFP should be administered together. The INR may rebound up if FFP is given without vitamin K.

Evidence supporting this recommendation is of classes: A, B, C, D, R

**Heparins (Unfractionated and Low-Molecular-Weight Heparin) and Synthetic Pentasaccharide (Fondaparinux)**

**8. Introduction**

Heparins (UFH, LMWH) anticoagulant effect is due to the presence of a pentasaccharide sequence which potentiates the action of antithrombin III leading to inactivation of several clotting factors – primarily factors Xa and IIa. Heparins have relatively rapid onset of action compared to warfarin and are often the first drug used in acute thrombotic situations.
Algorithm Annotations (cont)

UFH is derived from porcine or bovine sources. It has variable absorption, metabolism, pharmacokinetics and effects on anticoagulation. Monitoring is required in most patients treated with this drug.

LMWH are depolymerized byproducts of UFH. Pharmacological advantages of LMWH relate to superior absorption and consistent dose effect response.

Fondaparinux is a synthetic compound composed of the essential pentasaccharide sequence.

9. Indications

Indications for use of UFH, LMWH, and fondaparinux are outlined in ICSI guidelines related to this supplement.

10. Contraindications

A. Active major bleeding including intracerebral hemorrhage within past two weeks, subarachnoid hemorrhage until definitively treated
B. Hypersensitivity to heparin or pork products
C. Heparin-induced thrombocytopenia (HIT)
D. Thrombolytics given within past 24 hours for acute stroke
E. Renal failure (LMWH and fondaparinux)
F. Fondaparinux has a long elimination half-life and there is no antidote for reversal, therefore patients who may require rapid reversal are not candidates for this therapy.

11. Precautions

A. Active or history of recent gastrointestinal ulceration and hemorrhage
B. Bacterial endocarditis
C. Bleeding diathesis
D. Concomitant therapy with agents that inhibit platelets
E. Congenital or acquired bleeding disorders
F. Hemorrhagic stroke
G. Status post brain, spinal, or ophthalmologic surgery
H. Uncontrolled arterial hypertension
I. Diabetic retinopathy

12. Adverse Effects

A. Bleeding

Risk of bleeding increases with treatment-related factors such as dose, duration, and use of thrombolytics and/or antiplatelet agents, and patient-related factors including age over 70 years, recent trauma or surgery, coagulopathy, peptic ulcer, neoplasm, or renal failure.

Evidence supporting this recommendation is of classes: A, R
B. Adverse Effects in Pregnancy

UFH and LMWH do not cross the placenta and therefore do not cause teratogenicity or fetal bleeding, though bleeding at the uteroplacental junction is possible. Heparin is not secreted in breast milk and can be given safely to nursing mothers.

Major bleeding occurs at similar rates in pregnant and non-pregnant women receiving heparin. LMWHs cause less HIT and bone loss during pregnancy than UFH.

When possible, patients using UFH or a LMWH should have a planned delivery. UFH should be discontinued 6 hours prior to a planned delivery. LMWH should be discontinued 24 hours prior to a planned delivery.

The pharmacokinetics of LMWH in pregnancy are significantly altered. Consideration should be given to monitoring the antifactor Xa activity at 12-15 weeks and 30-33 weeks.

A recent study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the FDA and the manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valve patients who are pregnant. However, multiple registries of other heart valve patients have shown no such problems with therapeutic LMWH therapy. The workgroup feels that, although LMWH use is likely as safe as the alternative (bridging with UFH), patients should be made aware of this area of controversy before LMWH is used.

Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert.

There is limited data on use of fondaparinux in pregnancy. It is unknown if fondaparinux is excreted in human breast milk. Animal studies have been positive for excretion.

Evidence supporting this recommendation is of class: R

C. HIT

HIT is an immune-mediated reaction to heparins. It occurs in 2-3% of patients treated with UFH and < 1% of patients treated with LMWH. This syndrome can be associated with paradoxical increased risk for venous and arterial thrombosis. Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent 100 days. Patients with a history of HIT should not be treated with UFH or LMWH.

Patients who develop a greater than 50% decrease in platelet count from baseline labs or absolute platelet count less than 100,000 mm$^3$ while on heparin should have their heparin stopped while antibody testing for HIT is performed. Direct thrombin inhibitors (DTIs) are the alternative anticoagulant of choice for patients with HIT. Three brands are FDA approved: lepirudin (Refludan®), argatroban, and most recently, bivalirudin (Angiomax®).

Although in vitro data has not demonstrated cross reactivity of fondaparinux with HIT antibodies, additional studies are needed before its use can be considered. Thrombocytopenia can occur in patients treated with fondaparinux.

Please refer to Annotation Appendix G, "Direct Thrombin Inhibitors" for more information.

Evidence supporting this recommendation is of classes: C, D, R
Algorithm Annotations (cont)  

**UNFRACTIONATED HEPARIN**

13. **Dosing**

A. **General Principles of Adult UFH Dosing**

1. Weight-based, institution-specific nomograms are strongly recommended for patients on therapeutic intravenous UFH. Each institution must develop its own nomograms based upon their unique specific therapeutic ranges. Please refer to Annotation Appendix F for an example of a heparin nomogram.

2. Before administering UFH, the patient’s height in centimeters and weight in kilograms, and any adverse reactions to drugs or food including a description of the reaction should be noted.

3. Before administering UFH, draw hemoglobin/hematocrit, platelet count, activated partial thromboplastin time (aPTT) and prothrombin time (PT) if not done at admission.

B. **Initiation of UFH**

1. An initial bolus dose of heparin is recommended followed by IV infusion with the exception of acute stroke. The use of heparin in patients with acute stroke is controversial. Please refer to the ICSI Diagnosis and Treatment of Ischemic Stroke guideline. Note the time of initial heparin bolus.

2. After initial IV bolus of heparin, begin maintenance drip per institutional protocols.

C. **Maintenance**

1. Obtain an aPTT level or heparin assay six hours after the initiation of IV heparin drip. Adjust the IV drip according to institutional protocols. (See Annotation Appendix F, "Example of a Heparin Nomogram.")

2. A standard weight-based protocol for heparin administration should not be used for patients receiving parenteral platelet receptor glycoprotein IIb/IIIa antagonist (abciximab or ReoPro®), tirofiban (Aggrastat®), eptifibatide (Integrelin®), and/or thrombolytics (alteplase or Activase®). Treating physicians should refer to the specific recommended protocols for treating patients using the package insert for the individual thrombolytic or other agent, or refer to their institution’s protocols.

**Evidence supporting this recommendation is of classes: A, B**

14. **Monitoring**

A. **Principles of Monitoring UFH Therapy**

1. UFH treatment of thrombosis can be monitored using an aPTT or heparin assay. The recommended test for monitoring UFH including the therapeutic range for the test should be provided by the laboratory. Of note, aPTT results vary among institutions due to differences in laboratory instruments and reagents.

**Evidence supporting this recommendation is of classes: B, R**
2. Patients receiving UFH or a LMWH should be monitored for heparin-induced thrombocytopenia (HIT) with a platelet count beginning at baseline, then every other day. A platelet count of < 100,000 mm$^3$ or < 50% of baseline may indicate the development of HIT. See Annotation 12C for more information.

Note: Patients who have not received heparin within the previous 3 months are unlikely to develop HIT within the first 3 days of treatment – however, patients who have received heparin within 3 months may develop HIT more rapidly. Based on this information, the workgroup had previously recommended that patients who had received heparin within the past 3 months have their platelet count monitored beginning on day 3 and that patients who had not received heparin within the past 3 months have their platelet count monitored beginning on day 5. Unfortunately, patients are not always aware that they have received heparin (with surgery, central IV catheters, etc.) For the sake of safety and simplicity, the workgroup now recommends a platelet count every other day for all patients receiving UFH or a LMWH.

15. Correction of Supratherapeutic Anticoagulation Caused by UFH

Serious bleeding is an indication for reversal of heparin therapy. To achieve reversal, protamine sulfate is administered by slow IV infusion over 10 minutes as follows:

Hourly UFH rate (units) x 1.75 = protamine dose (mg)

Hypotension is an adverse effect of protamine treatment. Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin).

Evidence supporting this recommendation is of class: R

Low-Molecular-Weight Heparin

16. Dosing

General Principles of Adult Dosing LMWH

1. Therapeutic doses of a LMWH are different from prophylactic doses.

2. Doses of different types of heparins are not interchangeable.

3. The anticoagulant effect of LMWH can extend beyond 24 hours after administration.

4. The dose should be modified for patients with impaired renal function. LMWH are relatively contraindicated in patients with a creatinine greater than or equal to 2.0 mg/dL or who are receiving dialysis.

5. The optimal dose of LMWH has not been established in patients with low body weight (less than 50 kg), obesity, renal insufficiency, or pregnancy. It may be necessary to monitor the anti-Xa level in these patients.

Evidence supporting this recommendation is of classes: A, D, R
### Table 3: Therapeutic Dosing of LMWH

<table>
<thead>
<tr>
<th>FDA Approved Indications</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
</table>
| DVT and/or pulmonary embolism (PE) | • 1 mg/kg q 12h with transition to warfarin; approved for both inpatient and outpatient use  
• 1.5 mg/kg QD with transition to warfarin – inpatient only | Not approved | 175 anti-Xa IU/kg QD for ≥ 6 days with transition to warfarin |
| Unstable Angina/Non-Q-wave MI | 1 mg/kg q 12h and ASA (100-325 mg) for 2-8 d | 120 IU/kg q 12h and ASA for 5-8 days | Not approved |
| Notes | | | May interfere with PT/INR |

### Table 4: Prophylactic Dosing of LMWH

<table>
<thead>
<tr>
<th>FDA Approved Indications</th>
<th>Enoxaparin</th>
<th>Dalteparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
</table>
| Hip replacement | 30 mg 12-24h post-op and q 12h for up to 14 days (avg. 7-10 d); or 40 mg 12h pre-op and QD for 3 wks | 2500 IU 2h pre-op*  
2500 IU evening post-op, then 5000 IU QD for 5-9 d | Not approved |
| Knee replacement | same as hip replacement dosing | Not approved | Not approved |
| Abdominal surgery (general surgery) | 40 mg 2h pre-op then QD for 7-10 days | 2500-5000 IU pre-op*  
QD for 5-10 days post-op | Not approved |

*Standard practice in the U.S. is dosing dalteparin starting post-op.

Please refer to the ICSI Venous Thromboembolism Prophylaxis for Surgical/Trauma Patients guideline.
17. Monitoring

A. Principles of Monitoring
   1. In most clinical situations, monitoring of LMWH is not required.
   2. Indications for monitoring of LMWH include renal insufficiency (calculated creatinine clearance < 30), obesity, very low body weight, and pregnancy. To calculate the estimated creatinine clearance, use the Cockcroft-Gault equation as follows:
      
      In men:
      
      \[
      \text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg}}{(72 \times \text{serum creatinine})}
      \]
      
      In women:
      
      \[
      \text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg} \times 0.85}{(72 \times \text{serum creatinine})}
      \]
   3. The suggested therapeutic range for twice-daily dosing is 0.6 to 1.0 IU/ml obtained 4 hours after subcutaneous injection. One suggested target range for once-daily dosing is 1.0 to 2.0 IU/ml obtained 4 hours after subcutaneous injection.

B. Monitoring of LMWH
   1. The recommended test for monitoring LMWH is an antifactor Xa assay (heparin assay). An antifactor Xa assay standard curve must be constructed for each LMWH preparation used in the care system. Appropriate commercial controls can be used if available. Although the aPTT may be prolonged in patients on LMWH, it does not reliably reflect LMWH activity.
   2. Pretreatment and periodic platelet counts should be performed to identify developing HIT. (See Annotation #14, “Monitoring”.)

C. Key Patient Education Components: LMWH
   1. Over-the-counter and prescription drugs which should not be taken while on LMWH.
   2. Importance of understanding heparin assays, INRs and target ranges.
   3. Know and watch for signs of bleeding.
   4. Proper technique for injecting LMWH.
   5. Restrictions for other conditions including DVT, stroke, or CAD. Please refer to related ICSI guidelines for more information.
   6. Importance of adhering to prescribed regimen.

Evidence supporting this recommendation is of class: R
18. Correction of Supratherapeutic Anticoagulation Caused by LMWH

No agent, including FFP and Vitamin K is effective for complete reversal of supratherapeutic anticoagulation with LMWH. Reversal of LMWH with protamine sulfate may be incomplete, with neutralization of 60-75% at most. However, protamine should be considered for patients with severe life-threatening bleeding.

- The dose of protamine to reverse dalteparin is 1 mg protamine per 100 anti-Xa IU of dalteparin (Fragmin®). A second dose of protamine may be given at 100 anti-Xa IU of dalteparin if the aPTT measured at 2-4 hours after the first protamine infusion is prolonged.

- The dose of protamine needed to reverse enoxaparin is 1 mg protamine per 1 mg of enoxaparin (Lovenox®). A second dose of protamine may be given at 0.5 mg protamine per 1 mg enoxaparin if the aPTT measured 2-4 hours after the first protamine infusion is prolonged.

Evidence supporting this recommendation is of class: D

19. Precautions

A. Spinal or Epidural Anesthesia or Spinal Puncture

Bleeding or hematomas within the spinal column may result when a heparin product or fondaparinux is used concurrently with spinal or epidural anesthesia or spinal puncture. The risk for complication increases with placement or removal of catheters in the spinal canal and by traumatic or repeated epidural or spinal puncture. Use of other drugs affecting the blood clotting mechanism such as NSAIDs, platelet inhibitors, or other anticoagulants also increases the risk of complication.

1. If a continuous epidural anesthesia is administered, the decision to implement LMWH prophylaxis in the presence of an indwelling catheter must be made with extreme care. If LMWH prophylaxis is administered while the patient is receiving continuous epidural anesthesia, the patient must be monitored carefully for early signs of cord compression (e.g., progression of lower extremity numbness or weakness, or bowel or bladder dysfunction).

2. If LMWH prophylaxis is administered while the patient is receiving continuous epidural anesthesia, removal of the catheter should be delayed at least 8-12 hours after the dose of LMWH.

3. LMWH prophylaxis should be delayed 2 hours after placement of the spinal needle or removal of the catheter.

Evidence supporting this recommendation is of classes: D, R

B. Regional Anesthesia

Regional anesthesia should be avoided in patients with a history of abnormal bleeding or if taking medications that affect hemostasis (e.g., aspirin, NSAIDs, platelet inhibitors, warfarin).

1. If a regional anesthetic is administered, a single-dose spinal anesthetic is preferable to continuous epidural anesthesia.

2. If a LMWH is administered preoperatively, insertion of the spinal needle should be delayed at least 8-12 hours after the dose of LMWH. Regional anesthesia should be avoided if there is a hemorrhagic aspirate during insertion of the spinal needle.
C. Other Precautions
1. LMWH should not be administered by intramuscular injection.
2. Carefully monitor patients for possible spinal or epidural bleeding. Treat immediately if neurological impairment is detected.

20. Bridging Therapy
A. Patients on warfarin therapy for prevention of thromboembolism who need an invasive procedure may require parenteral anticoagulation perioperatively.

1. The decision to take a patient off warfarin and "bridge" with heparin is determined by the balance of bleeding risk due to the surgical procedure and clotting risk due to the underlying disorder.

2. Patients who have procedures that are of low bleeding risk (e.g., skin biopsies and most dental procedures) can be continued on uninterrupted warfarin anticoagulation.

3. An individual’s history of thromboembolism will assist with the decision-making.
   a. If a patient is at low thromboembolic risk (such as atrial fibrillation without prior CVA or remote history of a venous thromboembolic event), warfarin may be stopped 4-5 days prior to the procedure and resumed the evening of surgery.
   b. If a patient is at high thromboembolic risk (such as mechanical mitral valve with atrial fibrillation), bridging with therapeutic doses of LMWH may be indicated. Small cohort studies with dalteparin and enoxaparin have shown benefits in bridging.

A recent study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. Because of this, the FDA and manufacturer have warned that enoxaparin is not presently indicated for use in prophylaxis for heart valve patients who are pregnant. However, multiple registries of other heart valve patients have shown no such problems with therapeutic LMWH therapy. The workgroup feels that, although LMWH use is likely as safe as the alternative (UFH), patients should be made aware of this area of controversy before LMWH is used.

Patients with mechanical heart valves and who are pregnant are at high risk and should be managed by an anticoagulation expert.

   c. In general, therapeutic doses of UFH or LMWH have been used to bridge a patient perioperatively. In some cases, prophylactic dosing of heparin may be indicated. An example of prophylactic postoperative heparin dosing may be if the patient has an increased risk for postoperative DVT.

B. Due to the complexity of bridging therapy and the need for individualized treatment, consultation with a hematologist or expert in anticoagulation may be helpful.

C. If a patient is to receive bridging therapy, the patient or a caregiver must show proficiency in the injection technique and proficiency with adhering to the perioperative schedule.

D. The following schedule may be used if the decision to bridge has been made.
Table 5: Recommended Bridging Schedule

Please be aware that this schedule is not FDA-approved and there are no randomized controlled trials that have studied the efficacy of this schedule.

<table>
<thead>
<tr>
<th>Days Before Procedure</th>
<th>Warfarin</th>
<th>INR</th>
<th>LMWH * or Therapeutic UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 days prior to procedure</td>
<td>Last dose if target INR is 3.0</td>
<td>Check if not done within 2 weeks prior</td>
<td>4-5 days before procedure, start after first missed warfarin dose</td>
</tr>
<tr>
<td>4 days prior to procedure</td>
<td>Last dose if target INR is 2.5</td>
<td>Check if not done within 2 weeks prior</td>
<td>4-5 days before procedure, start after first missed warfarin dose</td>
</tr>
<tr>
<td>3 days prior to procedure</td>
<td>None</td>
<td>None</td>
<td>AM and PM dose</td>
</tr>
<tr>
<td>2 days prior to procedure</td>
<td>None</td>
<td>None</td>
<td>AM and PM dose</td>
</tr>
<tr>
<td>1 day prior to procedure</td>
<td>None</td>
<td>Check INR 1-2.5 mg po Vit K as needed if INR &gt; 1.5</td>
<td>AM dose only – at least 18 hours between dose and procedure</td>
</tr>
<tr>
<td>Procedure</td>
<td>Resume at regular dose</td>
<td>As indicated by surgeon</td>
<td>Start at least 12 hours post procedure – see Annotation #19 of guideline</td>
</tr>
<tr>
<td>1 day after procedure</td>
<td>Regular dose</td>
<td>Daily as needed – may be skipped</td>
<td>Restart if hemostasis achieved</td>
</tr>
<tr>
<td>2 days after procedure</td>
<td>Regular dose</td>
<td>Daily as needed</td>
<td>Restart if hemostasis achieved</td>
</tr>
<tr>
<td>3 days after procedure</td>
<td>Regular dose</td>
<td>Daily until INR &gt; minimum acceptable x 1 day</td>
<td>Continue until INR &gt; minimum acceptable x 2 day</td>
</tr>
</tbody>
</table>

* If enoxaparin (Lovenox®) is used as the LMWH, dosing is every 12h (a.m. and p.m.). Once-a-day dosing is used if the LMWH is tinzaparin (Innohep®) or dalteparin (Fragmin®).

E. For dental procedures, a review of the literature has shown that in most cases no change in warfarin is needed. It may be reasonable to allow the patient to "drift" to the lowest effective INR prior to a dental procedure. Local bleeding may be controlled with a variety of techniques including pressure, biting on tea bags, gelatin sponges and topical thrombin. Other means of local hemostasis control include tranexamic acid mouthwash or epsilon aminocaproic acid packing.

Evidence supporting this recommendation is of classes: D, R

**SYNTHETIC PENTASACCHARIDE (FONDAPARINUX)**

21. Dosing

General Principles of Adult Dosing Fondaparinux

A. Current FDA approved indication is limited to prophylaxis of venous thrombosis in patients undergoing surgery for hip fracture or hip or knee replacement.
Algorithm Annotations (cont)

B. Therapeutic doses are different than prophylactic dosing.

C. Fondaparinux is not recommended for patients with platelets less than 100,000 mm$^3$ or for those weighing less than 50 kg.

D. Dose should be modified in patients with renal impairment, however, should not be used in dialysis-dependent patients.

Table 6: FDA Approval Status, Indications, and Dosing of Fondaparinux

<table>
<thead>
<tr>
<th>FDA approved indication (adult)</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip-fracture surgery, hip/knee replacement surgery</td>
<td>2.5 mg SC once daily</td>
</tr>
<tr>
<td>Therapy for deep vein thrombosis</td>
<td>Not FDA approved</td>
</tr>
</tbody>
</table>

Evidence supporting this recommendation is of classes: A, M

22. Monitoring

The heparin assay (anti factor Xa) has been used to monitor effects of fondaparinux, however, in most clinical situations, monitoring may not be necessary.

Fondaparinux may cause transient elevations in serum aminotransferases. This effect is reversible and routine monitoring is not recommended.

Additional information on fondaparinux is included in the ICSI guideline on VTE Prophylaxis for Surgical/Trauma Patients guideline.
Annotation Appendix A – Risk Factors for Bleeding During Warfarin Therapy

Note: Some risk factors for bleeding, such as age, atrial fibrillation and hypertension, are also risk factors for thrombosis.

Patient-Related Risk Factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>recent MI, atrial fibrillation, hypertension</td>
</tr>
<tr>
<td>Endocrine</td>
<td>diabetes</td>
</tr>
<tr>
<td>GI</td>
<td>history of GI hemorrhage, active peptic ulcer disease, hepatic insufficiency</td>
</tr>
<tr>
<td>Hematologic/</td>
<td>anemia (HCT &lt; 30), thrombocytopenia (plt &lt; 50,000), platelet dysfunction,</td>
</tr>
<tr>
<td>Oncologic</td>
<td>coagulation defect, underlying malignancy</td>
</tr>
<tr>
<td>Neurologic</td>
<td>history of stroke, dementia, cognitive, or psychological impairment</td>
</tr>
<tr>
<td>Renal</td>
<td>renal insufficiency, current uremia</td>
</tr>
<tr>
<td>Trauma</td>
<td>recent trauma, history of falls (&gt; 3/year within previous year or recurrent,</td>
</tr>
<tr>
<td></td>
<td>injurious falls)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>excessive alcohol intake</td>
</tr>
<tr>
<td>Medications/</td>
<td>use of other medications, such as NSAIDs, or “natural remedies” that</td>
</tr>
<tr>
<td>Natural Remedies</td>
<td>interfere with hemostasis; increasing number of medications or “natural</td>
</tr>
<tr>
<td></td>
<td>remedies”</td>
</tr>
</tbody>
</table>

Anticoagulation Treatment-Related Risk Factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>increased risk during initial 3 months of treatment, cumulative risk over time</td>
</tr>
<tr>
<td>Intensity</td>
<td>INR &gt; 4.0</td>
</tr>
<tr>
<td>Variability of Control</td>
<td>adequacy of education, support, monitoring and follow-up</td>
</tr>
</tbody>
</table>

For patients who are otherwise deemed safe for outpatient warfarin therapy, the following risk factors are helpful to estimate an individual patient’s risk of bleeding. There is no published research to estimate the risk of bleeding for an unscreened patient. Therefore, clinical judgment with careful attention to contraindications to warfarin and risk factors for bleeding remains essential for the selection of patients appropriate for warfarin.

Risk of Bleeding: Prediction Rule for Selected Patients Otherwise Safe for Warfarin Therapy

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Sum of Risk Factors</th>
<th>Risk classification</th>
<th>Risk of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65</td>
<td></td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td></td>
<td>Intermediate</td>
<td></td>
</tr>
<tr>
<td>History of GI bleeding</td>
<td></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Recent MI, Hct &lt; 30%, Cr &gt; 1.5 mg/dL, or diabetes mellitus</td>
<td></td>
<td></td>
<td>within 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>within 12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1-2</th>
<th>3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk classification</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Risk of major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>within 3 months</td>
<td>2%</td>
<td>5%</td>
<td>23%</td>
</tr>
<tr>
<td>within 12 months</td>
<td>3%</td>
<td>12%</td>
<td>48%</td>
</tr>
</tbody>
</table>
# Annotation Appendix B – Recommended Therapeutic Range for Oral Anticoagulation Therapy

## Anticoagulation Therapy Supplement

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMI (to prevent systemic embolism)*</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Valvular (rheumatic) heart disease</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Mechanical prosthetic valves (high risk)</td>
<td>3.0</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic positions</td>
<td>2.5</td>
<td>2.0-3.0</td>
</tr>
</tbody>
</table>

*If oral anticoagulant therapy is elected to prevent recurrent myocardial infarction, an INR of 2.5-3.5 is recommended. This is consistent with Food and Drug Administration recommendations.*
**Annotation Appendix C –**  
**Drug/Herbal Interactions with Warfarin**  
*Anticoagulation Therapy Supplement*

<table>
<thead>
<tr>
<th>Precipitating drug</th>
<th>Mechanism of interaction</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen*</td>
<td>May increase potential for bleeding. Exaggerates the effects of warfarin in a dose-dependent fashion. Unknown mechanism of interaction.</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Large intermittent doses of alcohol cause some inhibition of warfarin metabolism. Intermediate use (2-3 glasses of alcohol a day) probably does not alter warfarin metabolism.</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Inhibits warfarin metabolism. May require decrease in warfarin dose.</td>
<td></td>
</tr>
<tr>
<td>Antacids</td>
<td>Inhibit the absorption of warfarin from the GI tract. When used in combination, administer warfarin at least 2 hrs prior to antacids or 4 hrs after antacids.</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Low-dose aspirin may be justified for some clinical indications for additional anticoagulant effects. Prolongation of prothrombin time may occur at high doses (&gt;3 grams) of aspirin.</td>
<td></td>
</tr>
<tr>
<td>Barbituates</td>
<td>Induce metabolism of warfarin. Require increase in warfarin dose over several weeks.</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Induces metabolism of warfarin. Requires increase in warfarin dose over several weeks.</td>
<td></td>
</tr>
<tr>
<td>Celecoxib (Celebrex®)</td>
<td>Can increase a patient’s risk of bleeding while on concomitant warfarin therapy. The likely mechanism of action is via competition for metabolism through cytochrome P450 2C9 enzymes.</td>
<td></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Cephalosporins interfere with vitamin K-producing bacteria in the gut. Use in combination is safe in most situations, provided vitamin K intake is normal. Direct prolongation of prothrombin time affects liver enzyme clotting factors. Cephalosporins with an N-Methylthiotetrazol (N-MTT) side chain have the most pronounced interaction – examples are cefotetan, cefamandole, cefoperazone.</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Binds warfarin in the gut and inhibits total warfarin absorption. Administer warfarin at least 2 hrs prior to cholestyramine or 6 hours after cholestyramine.</td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Inhibits warfarin metabolism. Substitute other H2 antagonists, e.g., ranitidine, famotidine, and nizatidine.</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Negative effect on INR option for patients who are allergic to lactams and provides an alternative to metronidazole for some anaerobic infections.</td>
<td></td>
</tr>
<tr>
<td>Colestipol</td>
<td>Binds warfarin in the gut and inhibits total warfarin absorption. Administer warfarin at least 2 hrs prior to colestipol or 6 hrs after colestipol.</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Cyclosporine inhibits warfarin by an unknown mechanism. An increase in dose may be required.</td>
<td></td>
</tr>
<tr>
<td>Disulfuram</td>
<td>Inhibits metabolism of warfarin. Avoid using in combination if possible, otherwise a decrease in warfarin dose may be required when initiating disulfuram therapy. When stopping disulfuram therapy, an increase in warfarin dose may be required.</td>
<td></td>
</tr>
<tr>
<td>Estrogens, oral contraceptives</td>
<td>Estrogens induce coagulant factors. Estrogens increase the risk for clot formation and decrease the effects of warfarin.</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Unknown mechanism due to poor documentation. Interaction is usually dose related.</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>Prolongation of prothrombin time. Prolongation of INR 10-20% of aPTT is in the therapeutic range.</td>
<td></td>
</tr>
<tr>
<td>Indomethacin (NSAIDs)</td>
<td>Inhibits platelet aggregation, increasing potential for bleeding.</td>
<td></td>
</tr>
<tr>
<td>Imidazoles (fluconazole, itraconazole, ketoconazole.)</td>
<td>Inhibits warfarin metabolism. Avoid if possible – clinically significant interaction. Otherwise may have to decrease warfarin dose up to 50% while giving an imidazole.</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Unknown: may inhibit warfarin metabolism, may be more common in slow acetylators.</td>
<td></td>
</tr>
</tbody>
</table>

### Precipitating drug | Mechanism of interaction
--- | ---
**Lovastatin** | Unknown mechanism. A decrease in warfarin dose may be required.
**Macrolides** | Erythromycin inhibits two enzymes that degrade warfarin causing significant elevations of INR. Avoid if possible, or consider a decrease in warfarin dose up to 25-50% while giving erythromycin. Clarithromycin moderately increases INR. Azithromycin is least likely to alter the INR.
**Metronidazole** | Inhibits metabolism of warfarin and substantially raises INR. Avoid if possible or decrease warfarin by up to 50% while giving metronidazole. This applies to oral, not topical therapy.
**Nitrofurantoin** | Not likely to alter INR. Consider for use in UTI as a substitute for sulfia or quinolines.
**Omeprazole** | Inhibits warfarin metabolism although moderate clinical significance.
**Penicillins** | Generally have little effect on INR. Additional monitoring generally not needed unless high doses are used more than 7 days. Nafcillin and dicloxacillin may decrease the INR and require a dose increase of warfarin.
**Phenylbutazone** | Inhibits warfarin metabolism. Alters protein binding of warfarin.
**Phenytoin** | When adding phenytoin to a patient currently receiving warfarin therapy, may see an initial inhibition of warfarin metabolism (potentiation of warfarin), followed by induction of warfarin metabolism. An increase or decrease in warfarin dose may be required. Monitor INR closely.
**Propranolol** | Unknown – Usually insignificant.
**Quinidine** | Unknown – May require decrease in dose of warfarin.
**Quinolones** | Generally inhibits warfarin metabolism, but variation exists. Avoid if possible. If it cannot be avoided, decrease warfarin dose up to 50% while giving a quinolone. Ciprofloxacin and norfloxacin have been reported to elevate INRs. Gatifloxacin, levofloxacin, and ofloxacin appear to be less prone to interfere with warfarin. INR should be monitored, particularly with quinolines known to interfere with warfarin.
**Rifampin** | Induces metabolism of warfarin. Careful monitoring of INR and a dose increase of warfarin (20%-50%) are required. The interaction is maximal in 1-2 weeks following addition of rifampin.
**Rofecoxib (Vioxx®)** | INR values should be closely monitored whenever rofecoxib is initiated or changed. Case reports suggest possible drug interaction.
**Sucralfate** | Altered absorption of warfarin. Minor interaction, change in warfarin dose usually not required.
**Sulfamethoxazole** | Sulfamethoxazole inhibits warfarin metabolism and delays warfarin protein binding. A decrease in warfarin dose may be required. Monitor INR within 3-5 days of starting, at least weekly during treatment and again one week following.
**Sulfinpyrazone** | Alters protein binding of warfarin. Inhibits metabolism. Antiplatelet effect. Avoid using in combination, otherwise may require a decrease in warfarin dose.
**Sulfonylureas (glipizide, glyburide, chlorpropamide, tolbutamide)** | Alters protein binding of warfarin. Avoid using in combination if possible. Otherwise, a decrease in warfarin dose may be required.
**Tetracycline** | Tetracycline interferes with vitamin K-producing bacteria in the gut. Safe, in most situations, when used in combination and provided vitamin K intake is normal.
**Sulfamethoxazole** | Sulfamethoxazole inhibits warfarin metabolism and delays warfarin protein binding. A decrease in warfarin dose may be required. Monitor INR within 3-5 days of starting, at least weekly during treatment and again one week following.
**Trimethoprim-sulfamethoxazole** | Inhibits warfarin metabolism. Avoid if possible. Otherwise decrease warfarin dose up to 50% while using in combination. (Trimethoprim, alone, does not appear to interact with warfarin.)
**Vitamin K (phytonadione)** | Vitamin K inhibits effectiveness of warfarin. Avoid changes in vitamin K intake. Know all sources of vitamin K: multivitamins, nutritional supplements, other over-the-counter products.
## Annotation Appendix C – Drug/Herbal Interactions with Warfarin (cont)

<table>
<thead>
<tr>
<th>Herb</th>
<th>Mechanism of Potential Interaction</th>
<th>Clinical Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angelica Root</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Anise</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Arnica Flower</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Asafoetida</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Bogbean</td>
<td>Unknown mechanism</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Borage Seed Oil</td>
<td>Contains γ - linoleic acid, which may ↑ INR</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Bromelain</td>
<td>Exhibits anti-platelet activity</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Capsicum</td>
<td>Decreases blood coagulation</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Celery</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Clove</td>
<td>Exhibits anti-platelet activity</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Coenzyme Q&lt;sub&gt;10&lt;/sub&gt;</td>
<td>Structurally related to menaquinone (Vit K&lt;sub&gt;3&lt;/sub&gt;) and may have procoagulant effects</td>
<td>↓ INR, avoid combination*</td>
</tr>
<tr>
<td>Danshen</td>
<td>Inhibits warfarin metabolism, inhibits platelet aggregation</td>
<td>↑ INR, ↑ Risk of bleeding, avoid combination*</td>
</tr>
<tr>
<td>Devil’s Claw</td>
<td>Unknown mechanism</td>
<td>↑ Risk of bleeding, avoid combination</td>
</tr>
<tr>
<td>Dong Quai</td>
<td>Contains at least 6 coumarin derivatives, inhibits platelet aggregation</td>
<td>↑ INR, ↑ Risk of bleeding, avoid combination*</td>
</tr>
<tr>
<td>Evening Primrose Oil</td>
<td>Reduced platelet aggregation</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Inhibits platelet release and aggregation</td>
<td>↑ Risk of bleeding, avoid combination*</td>
</tr>
<tr>
<td>Garlic</td>
<td>Interrupts thromboxane synthesis, thereby inhibiting platelet function</td>
<td>↑ Risk of bleeding, avoid combination*</td>
</tr>
<tr>
<td>Ginger</td>
<td>Interrupts thromboxane synthesis, thereby inhibiting platelet function</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Decreases platelet aggregation</td>
<td>↑ Risk of bleeding, avoid combination*</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Mechanism unknown, case reports of ↓ INR</td>
<td>↓ INR, avoid combination*</td>
</tr>
<tr>
<td>Green Tea</td>
<td>Dried green tea leaves contain substantial amounts of Vit K. Brewed green tea is generally not considered a significant source, however, large amounts may be of concern.</td>
<td>↓ INR with large amounts of herb</td>
</tr>
<tr>
<td>Horse Chestnut</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Licorice Root</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Lovage Root</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Meadowsweet</td>
<td>Contains high concentration of salicylate</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Papain</td>
<td>Mechanism unknown</td>
<td>↑ INR, avoid combination*</td>
</tr>
<tr>
<td>Parsley</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Passionflower Herb</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Poplar</td>
<td>Contains high concentration of salicylate</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Quassia</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Red Clover</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Rue</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Sweet Clover</td>
<td>Contains coumarin or coumarin derivative</td>
<td>↑ INR</td>
</tr>
<tr>
<td>Tumeric</td>
<td>Exhibits anti-platelet activity</td>
<td>↑ Risk of bleeding</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>May inhibit vitamin K activity. Not all patients have interaction</td>
<td>↑ INR, more likely if dose &gt; 400 IU / day</td>
</tr>
<tr>
<td>Willow Bark</td>
<td>Contains high concentration of salicylate</td>
<td>↑ Risk of bleeding</td>
</tr>
</tbody>
</table>

*Drugs in bold have had a documented report of potential interaction.

**TABLE IS NOT ALL-INCLUSIVE**

Annotation Appendix D –
Endogenous Interactions with Warfarin

Endogenous Interactions with Warfarin
A. Factors Associated with Decreased PT Response
   Decreased INR
   - edema
   - hereditary coumarin resistance
   - hyperlipemia
   - hypothyroidism

B. Factors Associated with Increased PT Response
   Increased INR
   - cancer
   - collagen disease
   - congestive heart failure
   - diarrhea
   - elevated temperature
   - hepatic disorders (infectious
     hepatitis, jaundice)
   - hyperthyroidism
   - poor nutritional state
   - steatorrhea
   - vitamin K deficiency
Annotation Appendix E – Patient Education
Guide to Warfarin Therapy

I. WARFARIN (WAR-far-in):
   A. Keeps blood clots from forming or getting larger.
   B. Belongs to a class of drugs called anticoagulants (“blood thinners”).

II. BRAND NAME(S):
   A. Coumadin®

III. WHEN YOU SHOULD NOT USE THIS MEDICINE:
   You should not use warfarin if you have had an allergic reaction to it. You should not use warfarin if you are pregnant or are planning to become pregnant.

IV. HOW TO USE AND STORE THIS MEDICINE:
   A. Tablets
      1. Your doctor will tell you how much to take and how often.
      2. May be taken with or without food.
      3. Store at room temperature, away from heat, light, and moisture.
      4. Keep all medicine out of the reach of children.
   
      If you miss a dose: Take the missed dose as soon as possible. If you do not remember until the next day, skip the missed dose. Only take your usual dose for the day. You should not use two doses at the same time.

V. DRUGS AND FOODS TO AVOID:
   A. Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
   B. Many medicines can change the way warfarin works. Give your doctor a list of all medicines you take.
   C. Make sure your doctor knows if you are taking aspirin or products that contain aspirin (such as medicines for colds or pain relief.)
   D. Avoid drinking large amounts of alcohol.
   E. Certain foods will change the way this medicine works. Do not change your diet while taking warfarin. Foods that contain vitamin K (such as lettuce, spinach, broccoli, cabbage, cauliflower, or liver) decrease the anti-clotting effects of this medicine. If you eat foods that have vitamin K, do not change the amount of these foods that you normally eat each day. If your doctor provides you with a special diet, follow it closely.

VI. WARNINGS:
   A. It is very important to have regular blood tests done while taking this medicine to determine the proper and safe dose. It is common while taking this medicine to have your dose changed.
   B. You should carry an identification card that shows that you are taking warfarin.
   C. If you are pregnant or breastfeeding, talk with your doctor before taking this medicine. If you become pregnant while being treated with this medicine, tell your doctor right away.
D. Make sure your doctor knows if you have bleeding ulcers, heavy menstrual periods, infections, liver or kidney problems, high blood pressure, or any other medical problems.

E. Make sure your doctor or dentist knows you are taking warfarin before you have any surgery or dental work.

VII. SIDE EFFECTS:

A. Call your doctor right away if you have any of these side effects:
   1. Bleeding from the gums or nose,
   2. Coughing up blood,
   3. Red or black bowel movements,
   4. Red or dark-brown colored urine,
   5. Unusually heavy menstrual bleeding,
   6. Heavy bleeding from cuts or wounds that does not stop,
   7. Easy bruising, purple spots on the skin,
   8. Severe headache.

B. If you have problems with these less serious side effects, tell your doctor:
   1. Poor appetite,
   2. Mild stomach cramps,
   3. Upset stomach, or
   4. Hair loss.

Used with permission from Mayo Clinic.
Several protocols for managing heparin therapy have been shown to more rapidly achieve therapeutic anticoagulation (as measured by aPTT levels) versus historical controls. Raschke, et al. developed the protocol summarized below.

Loading dose: 80 units/kg

Initial maintenance dose: 18 units/kg/hour

**Dosage Adjustments:**

<table>
<thead>
<tr>
<th>aPTT level*</th>
<th>Dosage Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 35 seconds</td>
<td>80 units/kg bolus, then increase infusion rate by 4 units /kg/hour</td>
</tr>
<tr>
<td>35-45 seconds</td>
<td>40 units/kg bolus, then increase infusion rate by 2 units/kg/hour</td>
</tr>
<tr>
<td>46-75 seconds</td>
<td>no change</td>
</tr>
<tr>
<td>71-90 seconds</td>
<td>decrease infusion rate by 2 units/kg/hour</td>
</tr>
<tr>
<td>&gt; 90 seconds</td>
<td>hold infusion 1 hour, then decrease infusion rate by 3 units/kg/hour</td>
</tr>
</tbody>
</table>

The aPTT levels are drawn 6 hours after any dosage change, adjusting heparin infusion by the sliding scale until aPTT is therapeutic (46 to 70 seconds). When 2 consecutive aPTTs are therapeutic, order aPTT (and re-adjust heparin drip as needed) every 24 hours.

*aPTT levels will vary depending on laboratory instruments and reagents. Each hospital must determine its own aPTT scale to the UFH therapeutic range and develop an appropriate aPTT nomogram based on this information.
DTIs are a relatively new class of anticoagulant drugs. They exert their effect by directly attaching to both free- and fibrin-bound thrombin. Potential advantages of these drugs over UFH are inhibition of fibrin (clot) bound thrombin, a more predictable anticoagulant response, and no effect on platelet factor 4. DTIs are presently approved for use in patients with active HIT and those with a previous history of HIT who require anticoagulation therapy. These drugs are also in varying stages of development for use in other thrombotic disease processes. Three available DTIs will be described for their use in HIT. It is strongly recommended that consultation with a hematologist or anticoagulation expert is done when using these new anticoagulant drugs because of both drug and disease complexities.

A. **Lepirudin (recombinant hirudin) (Refludan®)**

This is a potent specific inhibitor of thrombin that forms a slowly reversible complex with the enzyme by binding to both its active site and an exosite focus (bivalent effect). It is cleared predominantly by the kidneys with a half-life of 40 minutes post IV dose and 120 minutes post SQ dose. Its almost irreversible binding to thrombin has been associated with an increased risk of major bleeds in one study.

The drug is dosed at 0.4mg/kg bolus IV followed by 0.15mg/kg/hour IV with adjustments to maintain aPTT at 1.5-2.5 times the median of the laboratory normal range. This range may not be appropriate if the patient’s aPTT is elevated at baseline.

The ecarin clotting time and chromogenic hirudin assay have been shown to be superior tests for monitoring recombinant hirudin therapy. However, these tests are not yet widely available in clinical laboratories.

B. **Bivalirudin (Angiomax®)**

This is a semi-synthetic bivalent inhibitor of thrombin. However, unlike hirudin, bivalirudin produces only transient reversal of thrombin and a shorter half-life. It has minimal renal excretion.

Bivalirudin is dosed as a 1.0 mg/kg IV bolus followed by 2.5 mg/kg/hour for 4 hours followed by 0.2 mg/kg/hour infusion thereafter.

C. **Argatroban (Acova®)**

This is a small molecular weight reversible inhibitor of the active site of thrombin (univalent). This agent is excreted normally in patients with renal insufficiency, but the dose must be reduced in patients with hepatic failure.

Argatroban has a short half life (< 1 hr) and is dosed at 2 ug/kg/min with adjustments to maintain aPTT at 1.5-3.0 times normal (not to exceed 100s).

The major side effect of DTIs is bleeding. This appears to be more significant with the irreversible inhibitor Lepirudin and less so with the reversible inhibitors. There is no antidote for these medications should bleeding occur, which further supports the use of agents with a short half-life.


**Annotation Appendix H – Glossary of Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>Activated partial thromboplastin time</td>
</tr>
<tr>
<td>ASA</td>
<td>Aspirin</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>DTI</td>
<td>Direct thrombin inhibitor</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>FFP</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>HCT</td>
<td>Hematocrit</td>
</tr>
<tr>
<td>HIT</td>
<td>Heparin induced thrombocytopenia</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td></td>
<td>( \text{INR} = \left( \frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{\text{ISI}} )</td>
</tr>
<tr>
<td>ISI</td>
<td>International sensitivity index</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>ml</td>
<td>Milliliter</td>
</tr>
<tr>
<td>NSAID</td>
<td>Nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PCC</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>PE</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>PT</td>
<td>Prothrombin time</td>
</tr>
<tr>
<td>QOD</td>
<td>Every other day</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
</tbody>
</table>
Released in November for Third Edition.

*The next scheduled revision will occur within 12 months.*
In the interest of full disclosure, ICSI has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

Jill M. Strykowski, RPh, MS received honoraria from Aventis.

Bruce Burnett, MD is a member of the speakers bureau for Aventis, BMS and Astra Zeneca; a consultant for Aventis, Astra Zeneca, and Sauiflo-organor; receives grant support from Aventis and BMC, and receives research support from Astra Zeneca.

Steve Kopecky is a consultant for Glaxco Smith Kline and received research support from BMS.

ICSI’s conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.
I. CLASSES OF RESEARCH REPORTS

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial
Class B: Cohort study
Class C: Non-randomized trial with concurrent or historical controls
  Case-control study
  Study of sensitivity and specificity of a diagnostic test
  Population-based descriptive study
Class D: Cross-sectional study
  Case series
  Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M: Meta-analysis
  Systematic review
  Decision analysis
  Cost-effectiveness analysis
Class R: Consensus statement
  Consensus report
  Narrative review
Class X: Medical opinion
Discussion and References

WARFARIN

1. Introduction


3. Contraindications

C. Pregnancy

When administered between the 6th and 12th week of pregnancy, warfarin causes a characteristic embryopathy that includes nasal hypoplasia and stippled epiphyses in 4-5% of fetuses. Unlike warfarin embryopathy, which results primarily from exposure in the first trimester, CNS anomalies occur after exposure to warfarin at any time in the pregnancy and are more debilitating. CNS anomalies occur in about 3% of fetuses, and are thought to be the result of intracranial hemorrhages induced by the fetal hypercoagulable state.

If the mother is taking warfarin at the time of delivery, the rate of fetal intracranial hemorrhages during delivery is 12%. This percentage increases if forceps or other obstetrical maneuvers are required. The incidence of spontaneous abortions, stillbirths and neonatal deaths is 15% with exposure to warfarin at any time during the pregnancy.


D. Exclusion Criteria

Please refer to Discussion #12A on adverse effects/bleeding.

4. Adverse Effects

A. Bleeding

It is important to note that trials evaluating the safety and effectiveness of oral anticoagulants in patients with atrial fibrillation excluded 80% of patients on the basis of factors presumed to increase their risk of bleeding.

Some criteria have been validated as risk factors for bleeding. These include age of 65 years or older, history of gastrointestinal (GI) bleeding, hypertension, heart disease, cerebrovascular disease, and renal insufficiency.

Other criteria, such as noncompliance, unreliability, psychological problems, dementia, or other cognitive impairments, frequent or significant falls, excessive alcohol intake, or daily use of NSAIDs have not been validated as risk factors. However, their actual impact may have been underestimated because few, if any, patients with these criteria enrolled in the trials of potential risk factors. For example, Beyth, Quinn, and Landefeld’s index for predicting the risk of major bleeding in outpatients treated with warfarin was derived from patients deemed appropriate for outpatient anticoagulation by their personal physicians, with no description of the patients not enrolled in the trial.
The exclusion criteria in these trials that have not been validated as risk factors (noncompliance, unreliability, psychological problems, dementia, or other cognitive impairments, frequent or significant falls, excessive alcohol intake, or daily use of NSAIDs) should not be considered absolute contraindications to anticoagulant therapy in practice. However, few patients with these criteria have been formally studied, and the potential decreased risk of thromboembolism must be balanced against the potential increased risk of bleeding.

Patients treated with usual doses of warfarin have a 2-4% risk per year of bleeding episodes requiring transfusion, and a 0.2% risk per year of fatal hemorrhage. Risk factors for bleeding include patient-related factors and treatment-related factors. Patient-related factors include age, previous episodes of bleeding, anemia (HCT < 30), renal disease, history of GI hemorrhage, active peptic ulcer disease or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, and use of other medications or natural remedies. Treatment-related factors include duration, intensity and variability of warfarin treatment, and support patients receive from their providers and home environments. An expanded list of risk factors for bleeding is attached in Annotation Appendix A, "Risk Factors for Bleeding During Warfarin Therapy."


Findings from this and additional clinical trials are included in:


B. Skin Necrosis

Skin necrosis presenting with painful localized skin lesion (incidence 0.01%-0.1%) is associated with thrombosis of venules and capillaries within subcutaneous fat, usually within the first 3 days of therapy. It has been associated with protein C or protein S deficiency. In some cases, it may occur with large loading doses of warfarin, and is four times as common in women as in men. Skin necrosis has also been reported as a complication occurring in patients with HIT who are started on warfarin. Because of the extreme rarity of this complication, routine pre-testing for this condition in all individuals prior to initiation of oral anticoagulation is not advised.

When warfarin-induced skin necrosis is suspected, patients should be placed on heparin therapy. Warfarin has been successfully used in such cases by initiating very low doses while continuing heparin and gradually escalating the dose over several weeks to avoid an abrupt drop in protein C levels before coagulation factors levels are reduced.


Discussion and References (cont)

C. Purple Toe Syndrome

Purple toe syndrome or other manifestations of the release of systemic atherocholesterol microemboli, such as in renal failure or the release of cholesterol in plaques that have ulcerated in the aorta, are rare complications that usually occur 3-10 weeks after initiation of therapy.


D. Less Serious Adverse Effects


Cornbleet T, Hoit L. "Alopecia from coumarin." Arch Dermatol 75:440-41, 1957. (Class D)


5. Dosing


A. General Principles of Warfarin Dosing

Recent studies compared patients initiated on 10 mg versus 5 mg of warfarin. Although the 10 mg group achieved a therapeutic INR sooner (44% at 36 hours versus 8% and 36 hours), there was also a greater incidence of supratherapeutic anticoagulation in patients given the higher initial dose. A follow-up study of similar design showed equal efficacy in achieving a therapeutic INR for patients given 5 mg versus 10 mg initial warfarin dosing.


Findings from this and other clinical trials are included in:


1. Loading doses and rapid induction of warfarin should be avoided. Large doses of warfarin in the first 3 days of therapy will cause a quick initial reduction in both factor VII and protein C, as these substances have the shortest half-lives of all the vitamin K-dependent clotting factors. Low endogenous anticoagulant protein C levels in the first 3 doses of therapy may set up a hypercoagulable state. In addition, large doses of warfarin will also increase the risk of over-anticoagulation and subsequent bleeding.


2. A single target INR value should be used as a goal endpoint. The desired goal INR is indication-specific. For example, anticoagulation in persons with atrial fibrillation should be adjusted to a target INR of 2.5.


6. Some equivalency studies have shown that substitution of generic warfarin for brand name Coumadin® may provide equivalent anticoagulation response if the manufacturer of the generic warfarin has followed the standards set for the name brand.


7. **Drug Interactions: Rofecoxib (Vioxx®)**

   INR values should be closely monitored whenever rofecoxib is initiated or the dose is changed. Using single doses of warfarin 30 mg and rofecoxib 50 mg in healthy volunteers, INR values were increased by 11% compared to warfarin alone. In a 21-day multiple dose study, healthy study subjects stabilized on warfarin experienced a mean increase in INR of 8% when rofecoxib 25 mg daily was added to therapy.

**General**

Mechanisms of drug-drug interactions occur commonly by the cytochrome P450 enzyme metabolizing system. Metabolism of the object or substrate medication may either be induced or inhibited by the interacting drug. Induction will result in a diminished pharmacodynamic response, while inhibition will result in an increased pharmacodynamic response.
Discussion and References (cont)

Warfarin

Warfarin is a racemic mixture of both the weak anticoagulant R-warfarin and the stronger S-warfarin enantiomer. Each isomer is metabolized by a different isoenzyme; medications that inhibit or induce R-warfarin will have a weaker effect on S-warfarin.

The following table shows isoenzymes in which warfarin acts as a substrate. This table is useful in predicting unknown drug interactions if the metabolic properties of the interacting drug are known. Substrates can also act simultaneously as inhibitors or inducers of isoenzymes.

The response of warfarin (INR) should be measured within 4-7 days when an interacting drug is added, subtracted or has a dose change.

<table>
<thead>
<tr>
<th>Drug</th>
<th>IA2</th>
<th>IC9</th>
<th>IC19</th>
<th>ID6</th>
<th>IE1</th>
<th>IA4</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-warfarin</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>S-warfarin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Initiation of Warfarin


Blann A, Hewitt J, Siddiqui F, Bareford D. "Racial background is a determinant of average warfarin dose required to maintain the INR between 2.0 and 3.0." *Br J Haematol* 107:207-09, 1999. (Class D)


1. Average Daily Dosing Technique

Comparison between 10 mg and 5 mg loading doses demonstrates less excess anticoagulation with the 5 mg dose. Further, the 5 mg dose avoids a potential hypercoagulable state caused by decline in Protein C, an endogenous anticoagulant.


Comparison between 10 mg and 5 mg loading doses of warfarin does not result in a quicker therapeutic INR at day 4 or 5 with the higher dose.


2. Flexible Daily Dosing Technique

Formulas have been devised to predict dosing requirements form the early phase of warfarin therapy. One protocol used an initial 10 mg dose and predicted maintenance dosage based on the INR result on the second and third day of therapy.

Discussion and References (cont)  

Anticoagulation Therapy Supplement

6. Monitoring

A. Principles of Monitoring Warfarin Therapy

1. The INR is the preferred test for monitoring warfarin therapy despite several recognized limitations of the test, including instrumentation effect on the ISI and erroneous reporting of the ISI by the thromboplastin manufacturer.

   The INR = (Patient PT / Mean Normal PT) \( ^{ISI} \)

   Where "PT" is prothrombin time, and the "ISI" is the International Sensitivity Index assigned to the thromboplastin used in the test.


2. Patient samples should be collected in 109 mmol/L (3.2%) sodium citrate when INR testing is performed on anticoagulated plasma.

   Adcock DM, Kressin DC, Marlar RA. "Effect of 3.2% vs 3.8% sodium citrate concentration on routine coagulation testing." Am J Clin Pathol 107:105-10, 1997. (Class B)


   a. The volume of sodium citrate in blood tubes used for collection of plasma INR testing should be adjusted when the patient’s hematocrit is > 55%. Specimens with a high hematocrit will cause spuriously high INR values unless the citrate volume is adjusted.

      NCCLS. "Collection, transport, and processing of blood specimens for coagulation testing and general performance of coagulation assays; approved guideline – third edition." December 1998. (Class R)

   b. Anticoagulated whole blood may be stored spun or unspun at room temperature for up to 24 hours prior to testing.


   c. Sensitive thromboplastins (ISI values between 0.9 and 1.7) are recommended for INR testing. Thromboplastins with ISI values near 1.0 are preferred. Sensitive thromboplastin reagents potentially improve the precision of the INR test and broaden the range of PT ratios corresponding to a therapeutic INR.


4. Patients with a lupus anticoagulant may require a higher target therapeutic range than patients lacking a lupus anticoagulant.
Lupus anticoagulants can cause a prolongation of the PT and INR resulting in an overestimation of a patient’s anticoagulation. This effect is dependent on the thromboplastin that is used for the test.

Clinically significant alterations of the INR due to a lupus anticoagulant can occur during warfarin therapy despite a normal baseline PT/INR.

Measurement of chromogenic Factor X levels may be helpful in the monitoring of warfarin therapy in patients with lupus anticoagulant.


B. Options for Monitoring and Management


Beyth, et al., (133:2000) published a randomized control trial of 325 patients 65 years of age and older that compared patients whose warfarin was managed their personal physicians with patients whose was warfarin managed by anticoagulation clinics. The intervention group also received specific recommendations about modifiable risk-factors for bleeding (such as use of NSAIDs) and one-on-one teaching by a lay educator using a workbook specifically formatted for older adults. Patients were also coached to increase participation in their care, improve their information-seeking and communication skills, and trained to self-monitor their INRs using a portable home finger-stick monitor. After 6 months, the cumulative incidence of major bleeding was 12 % in the usual care group and 5.6% in the intervention group. Death and recurrent venous thromboembolism occurred with similar frequency in both groups.


Discussion and References (cont)

Anticoagulation Therapy Supplement

a. Whole blood analyzers typically using finger-stick, non-anticoagulated whole blood can be used for monitoring warfarin therapy. INR values outside of the therapeutic range (2.0-3.0) obtained using a whole blood, finger-stick method may show significant bias when compared to plasma-based INR results obtained on laboratory instruments.

An adequate quality program should be developed and followed for all whole blood testing.

If more than one testing method is used to follow warfarin therapy, comparative studies should be performed, and the results made available to the testing and treating practitioners.


d. The laboratory instrumentation used for INR testing may affect the ISI provided by the manufacturer.


2. Development and Support of Anticoagulation Clinics

The Anticoagulation Forum is an organization of anticoagulation clinics in the United States. The forum’s website at www.acforum.org is useful for locating and contacting anticoagulation clinics and related meetings across the country.

The National Certification Board for Anticoagulation Providers is a multidisciplinary group established in 1998 to develop, maintain, and foster the certification process in order to optimize care of patients receiving anticoagulation therapy. They can be contacted at:

National Board of Anticoagulation Providers
c/o Anticoagulation Forum
Boston University Medical Center
Room E-113
88 East Newton Street
Boston, MA 02118-2395

Additional resources on development and support of anticoagulation clinics include:


Additional information on support of anticoagulation clinics is available in a supplement of the journal, Chest. The citation is: American College of Chest Physicians. Sixth ACCP Consensus Conference on Antithrombotic Therapy. Chest January 2001 Supplement. To order the supplement, call 1-800-343-2227.
Discussion and References (cont)

7. Correction of Supratherapeutic Anticoagulation Caused by Warfarin

One must weigh the benefits of reversing anticoagulation with warfarin and associated decreased risk for bleeding against the risk of vitamin K-induced warfarin resistance and associated increased risk for thromboembolism. In general, withholding dosing of warfarin for an INR slightly above therapeutic range and adding a small dose of oral vitamin K can help prevent warfarin resistance.


Findings from this and other clinical trials are included in:


In 1998, Beyth, Quinn and Landefeld published a prediction rule for estimation of the risk of bleeding while on outpatient warfarin therapy. The prediction rule was derived from a cohort of 565 patients who started outpatient warfarin upon discharge from Brigham and Women’s Hospital between 1977 and 1983. The cohort was followed from 1983-1985. The prediction rule was then tested prospectively on a cohort of 264 consecutive patients who started outpatient warfarin therapy upon discharge from University Hospitals of Cleveland between April 1986 and April 1987. Patients were followed through June 1993 or until cessation of anticoagulation therapy or death.

It is worth noting that both cohorts were derived from patients who were deemed safe for outpatient warfarin therapy by their primary physicians. For patients who are otherwise deemed safe for outpatient warfarin therapy, the above risk factors are helpful to estimate an individual patient’s risk of bleeding.

There is no published research to estimate the risk of bleeding for an unscreened patient. Therefore, clinical judgment with careful attention to contraindications to warfarin and risk factors for bleeding (see above) remains essential for the selection of patients appropriate for warfarin therapy. As indications for warfarin and the duration of warfarin therapy expand, it has become even more important to design trials to estimate the risk of bleeding for all patients.


12. Adverse Effects

A. Bleeding

The rate of major bleeding associated with 5-10 days of IV unfractionated heparin in patients with acute venous thromboembolism (VTE) is 0.0-7.0% and the rate of fatal bleeding 0-2.0%. The rate of major bleeding associated with 5-10 days of sq low-molecular-weight heparin in patients with acute VTE is 0.0-0.8%. There is no increased risk of bleeding associated with short-term IV unfractionated heparin and subcutaneous low-molecular-weight heparins in patients with unstable angina.


Findings from this and other clinical trials are included and discussed in:


Findings from this and other clinical trials are included in:


B. Adverse Effects in Pregnancy

Unfractionated heparin does not cross the placenta and therefore does not cause teratogenicity or fetal bleeding, though bleeding at the uteroplacental junction is possible. Adverse outcomes are similar to those in untreated population.

Major bleeding occurs in about 2% of patients. This is similar to the rate of bleeding in nonpregnant patients.

HIT occurs in 1-3% of pregnant women on heparin therapy, a rate similar to nonpregnant patients. Alopecia and skin reactions including skin necrosis can occur.
Bone loss may occur in up to one-third of women receiving unfractionated heparin for more than 1 month, though the risk of symptomatic fractures is less than 2%. The radiographic evidence of bone loss is at least partially reversible, though it is unknown how long the increased risk of fractures persists.

Like unfractionated heparin, LMWH does not cross the placenta, though bleeding at the utero-placental junction is possible. Though LMWHs are free of teratogenic effects in rats, human data are limited.

Bleeding risks for the mother are similar to those with unfractionated heparin. Risks of HIT and bone loss are decreased with use of LMWH rather than UFH.


C. HIT

Thrombocytopenia can complicate heparin therapy. Both a non-immune and a more serious immune-mediated platelet-associate IgG reaction HIT have been described. If the patient has previously received heparin, especially within the past 100 days, thrombocytopenia may occur within hours or days. A retrospective study of 62 patients with serologically confirmed HIT found a 53% incidence of thrombosis in the month following diagnosis. UFH and LMWH should not be used to treat thrombosis in the setting of HIT. Heparin dependent antibodies do not always reappear with subsequent heparin use.


While uncommon, serious arterial or venous thrombosis can occur in the setting of thrombocytopenia. It may occur in up to 1% of patients treated with therapeutic doses of UFH for more than 5 days. LMWH can cross-react with UFH and should not be used to treat HIT.

DTIs are the treatment of choice for patients with HIT. Three brands are FDA approved: lepirudin (Refludan®), argatroban (Acova®), and most recently bivalirudin (Angiomax®). Patients who develop HIT without associated thrombosis will have a significant risk for thrombosis in the subsequent several months.


UNFRACTIONATED HEPARIN

13. Dosing

General Principles of Adult UFH Dosing

Several heparin therapy management protocols have been shown to achieve therapeutic anticoagulation (as measured by aPTT levels) more rapidly than historical controls. Several acceptable protocols...
Discussion and References (cont)

are discussed in the literature. These include a fixed initial maintenance dose, two levels of the initial
maintenance dose based on patient’s risk of bleeding, and several levels of the initial maintenance
dose based on patient’s body weight.

Cruickshank MK, Levine MN, Hirsh J, et al. "A standard heparin nomogram for the management of

Raschke RA, Reilly BM, Guidry JR, et al. "The weight-based heparin dosing nomogram compared with a

14. Monitoring

A. Laboratories recommending the aPTT for monitoring UFH should determine the therapeutic
range using plasma samples obtained from patients receiving UFH. The aPTT therapeutic range
should correspond to a plasma heparin concentration of 0.3 to 0.7 units/mL by an antifactor Xa
inhibition assay (0.2 to 0.4 units/mL by protamine titration assay).


Heparin assays are being increasingly used for monitoring UFHs in the treatment of venous
thromboembolism. The suggested target therapeutic range is 0.35 to 0.7 units/mL by the anti-
factor Xa inhibition assay. Monitoring unfractionated heparin using a heparin assay may be
indicated when the expected aPTT prolongation is not observed despite high doses of UFH
(greater than 35,000 U unfractionated heparin in 24 hours), when the pretreatment aPTT is
prolonged or when a lupus anticoagulant has been previously documented in the patient.

nisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety." Chest 119(1Suppl):
64S-94S, 2001. (Class R)

Olson JD, Arkin CF, Brandt JT, et al. "College of American pathologists conference XXXI on labo-
ratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy."
Arch Pathol Lab Med 122:782-98, 1998. (Class R)

15. Correction of Supratherapeutic Anticoagulation Caused by UFH


LOW-MOLECULAR-WEIGHT HEPARIN

16. Dosing

General Principles of Adult Dosing LMWH

1. LMWHs are identified and marketed as separate drugs because various methods of depolymer-
ization result in slightly different molecular weights and, therefore, slightly different pharmacokinetics among the various preparations. All are dosed in a fashion to give the same amount of
antifactor Xa activity, but can be different in their half-lives and clearances.

2. LMWH doses are not to be used interchangeably with either another LMWH or UFH. Doses of
different types of LMWH are not interchangeable.
**Discussion and References (cont)**


5. Dosing of LMWH should be modified for patients with impaired renal function. It may be necessary to reduce the recommended dose of LMWH for obese patients.


17. Monitoring


18. Correction of Supratherapeutic Anticoagulation Caused by LMWH

Reversal of supratherapeutic anticoagulation with protamine sulfate may be incomplete. However, it should be considered in patients with severe life threatening bleeding.


19. Precautions

A. Spinal or Epidural Anesthesia or Spinal Puncture

Bleeding or hematomas within the spinal column may result when the heparin product is used concurrently with spinal or epidural anesthesia or spinal puncture. Spinal cord paralysis can result from these conditions. The risk for complication increases with placement or removal of catheters in the spinal canal and by traumatic or repeated epidural or spinal puncture. Use of other drugs affecting the blood clotting mechanism, such as NSAIDs, platelet inhibitors, or other anticoagulants also increases the risk of complication.

Tryba M, Wedel DJ. “Central neuraxial block and low-molecular-weight heparin (enoxaparin): lessons learned from different dosage regimes in two continents.” *Reg Anesth* 100-04, 1997. (Class D)

Spinal hematomas after neuroaxial blockade are very rare (3 in 850,000 in one study) and therefore are difficult to attribute cause and effect. Vandermulen reviewed 61 cases of spinal hematoma associated with spinal or epidural anesthesia. Of these, 25 patients received heparin therapy around the time of the procedure. Fifteen experienced spinal hematoma immediately...
after epidural catheter removal. In a letter to the New England Journal of Medicine, Wyskowski noted that, to date, the FDA has received 43 reports of patients with spinal or epidural hematoma after receiving the LMWH enoxaparin. This has prompted the FDA to ask LMWH manufacturers to include warning labels for this complication.

Given these concerns, it is recommended that the first dose of LMWH not be given within 12 hours of spinal anesthesia. Also, LMWH should be withheld at least 12 hours before and at least 2 hours after removal of epidural catheters.


20. Bridging Therapy

A.3. An individual’s history of thromboembolism will assist with the decision-making.


D. Bridging Schedule

A comprehensive review of the literature regarding patients undergoing dental procedures demonstrated that risk of thromboembolism in patients off anticoagulation is far greater than risk of hemorrhage in patients that are fully anticoagulated. The author suggests that patients remain anticoagulated for their dental procedures and that local measures such as pressure, biting on tea bags, gelatin sponges, topical thrombin or tranexamic acid be used to control any potential bleeding.


SYNTHETIC PENTASACCHARIDE (FONDAPARINUX)

21. Dosing


This document provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.
# Recommended Website Resources

Note: Websites are listed in alphabetical order, not in order of work group preference.

<table>
<thead>
<tr>
<th>Website Sponsor</th>
<th>Target Audience</th>
<th>Description</th>
<th>Website Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulation Forum</td>
<td>Providers</td>
<td>The forum is an organization of anticoagulation clinics across the country. The site is useful for finding clinics in other states and professional meetings relevant to anticoagulation.</td>
<td><a href="http://www.acforum.org">www.acforum.org</a></td>
</tr>
<tr>
<td>Aventis Pharmaceuticals</td>
<td>Patients</td>
<td>Although a pharmaceutical company sponsors the site, it provides helpful patient-centered information on DVT risks, symptoms, treatment, and lifestyle change to prevent thrombosis. Also provides information on heart healthy lifestyles, news, and additional resources.</td>
<td><a href="http://www.thrombosisonline.com">www.thrombosisonline.com</a></td>
</tr>
<tr>
<td>CareInternet</td>
<td>Providers and patients</td>
<td>Resource on cardiovascular and respiratory diseases. All information is peer-reviewed by a select panel of professionals and lay persons. It includes information specific to antithrombotic therapy.</td>
<td><a href="http://www.careinternet.com">www.careinternet.com</a></td>
</tr>
<tr>
<td>The Natural Pharmacist</td>
<td>Providers and patients</td>
<td>The website is a searchable database of herbal therapy offering an unbiased, independent, integrated review of natural products. Users can find both negative and positive product reviews of natural therapies. Includes information on drug interactions with herbal preparations.</td>
<td><a href="http://www.TNP.com">www.TNP.com</a></td>
</tr>
</tbody>
</table>
Support for Implementation –
Recommended Educational Resources (cont)  Anticoagulation Therapy Supplement

RECOMMENDED WEBSITE RESOURCES (CONT)

These websites were reviewed by the ICSI Anticoagulation Therapy Supplement guideline work group as credible resources. ICSI does not have the authority to monitor the content of these sites. Any health-related information offered from these sites should not be interpreted as giving a diagnosis or treatment.

* Criteria for Selecting Websites

The preceding websites were selected by the Anticoagulation Therapy Supplement guideline work group as additional resources for practitioners and the public. The following criteria were considered in selecting these sites.

- The site contains information specific to the particular disease or condition addressed in the guideline.
- The site contains information that does not conflict with the guideline's recommendations.
- The information is accurate and/or factual. The author of the material or the sponsor of the site can be contacted by means other than e-mail. For example, a nurse line or other support is provided.
- The material includes the source/author, date and whether the information has been edited in any way. The site clearly states revision dates or the date the information was placed on the internet.
- The site sponsor is an objective group without an obvious or possible bias. For example, the site does not promote a product, service or other provider.
- The coverage of the topic is appropriate for the guideline's target audience. It is clearly written, well-organized and easy to read. The site is easy to navigate.