ICSI

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:
Antithrombotic Therapy Supplement

Seventh Edition
April 2009

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;
- health care teaching institutions;
- health care information technology departments;
- 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.

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Foreword

Scope and Target Population

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

Clinical Highlights and Recommendations

- 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, 13, 14, 15, 16, 27, 28, 30, 37, 38, 40, 47, 48, 50, 56, 57, 59)*
- 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/fondaparinux) should be used concomitant with warfarin. *(Annotation #7)*
- Loading doses of warfarin should be avoided. *(Annotation #7)*
- Many prescription medications and over-the-counter remedies, including dietary supplements and herbs, may alter the effectiveness of warfarin or vitamin K antagonists (detected by the INR) and/or reduce the effectiveness of platelets (not detected by the INR). *(Annotation #7, Appendices B, C, D)*
- Vitamin K may be used to reverse supratherapeutic anticoagulation with warfarin. The dose of vitamin K depends upon the degree of international/normalized ratio (INR) elevation and/or signs and symptoms of bleeding. Vitamin K can lead to warfarin resistance and subsequently to an increased risk of thromboembolism. *(Annotation #9)*
- 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 undergoing an invasive procedure. *(Annotations #11, 21, 25, 35, 45, 55, 64, Appendix D)*
- 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 #11, 21, 25, 35, 45, 55, 64, Appendix D)*
- Patients with mechanical heart valves who are pregnant have complex anticoagulation needs and should be managed by an anticoagulation expert. *(Annotations #4, 16)*

Related ICSI Scientific Documents

Guidelines

- Atrial Fibrillation
- Heart Failure in Adults
- Diagnosis and Initial Treatment of Ischemic Stroke
- Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)
- Venous Thromboembolism Diagnosis and Treatment
- Venous Thromboembolism Prophylaxis

Order Sets

- Admission for Ischemic Stroke for Patients Not Receiving tPA
- Admission for Ischemic Stroke for Patients Receiving tPA
- Admission to CCU for Acute Coronary Syndrome (ACS)
- Admission for Heart Failure
- Emergent Orders for Heart Failure
- Discharge for Heart Failure
- Venous Thromboembolism Prophylaxis for the Medically Ill Patient

Disclosure of Potential Conflict of Interest

ICSI has adopted a policy of transparency, disclosing potential conflict and competing interests of all individuals who participate in the development, revision and approval of ICSI documents (guidelines, order sets and protocols). This applies to all work groups (guidelines, order sets and protocols) and committees (Committee on Evidence-Based Practice, Cardiovascular Steering Committee, Women's Health Steering Committee, Preventive & Health Maintenance Steering Committee and Respiratory Steering Committee).

Participants must disclose any potential conflict and competing interests they or their dependents (spouse, dependent children, or others claimed as dependents) may have with any organization with commercial, proprietary, or political interests relevant to the topics covered by ICSI documents. Such disclosures will be shared with all individuals who prepare, review and approve ICSI documents.

No work group members have potential conflicts of interest to disclose.

Introduction to ICSI Document Development

This document was developed and/or revised by a multidisciplinary work group utilizing a defined process for literature search and review, document development and revision, as well as obtaining input from and responding to ICSI members.

For a description of ICSI's development and revision process, please see the Development and Revision Process for Guidelines, Order Sets and Protocols at http://www.icsi.org.

Evidence Grading System

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

Citations are listed in the guideline utilizing the format of *(Author, YYYY [report class])*. A full explanation of ICSI's Evidence Grading System can be found at http://www.icsi.org.

Algorithm Annotations

Introduction

The ICSI Antithrombotic Therapy Supplement has been developed as a resource for the use of antithrombotic drugs. This is a supplemental document that brings about consistency in recommendations that are common to the scope of related ICSI guidelines. See related ICSI scientific documents: Atrial Fibrillation, Heart Failure in Adults, Diagnosis and Initial Treatment of Ischemic Stroke, Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS), Venous Thromboembolism Diagnosis and Treatment and Venous Thromboembolism Prophylaxis.

Antithrombotic 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 few absolute contraindications to antithrombotic therapy with the exception of active life-threatening bleeding. The decision to treat a patient with antithrombotic drugs takes into account an individual patient's risk for thrombosis if not treated weighed against the risk of bleeding while on antithrombotic drug 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 antithrombotics.

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

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 and X, as well as the anticoagulant proteins C and S. The antithrombotic effect of warfarin is dependent on reduction of factor II (prothrombin), the factor with the longest half-life of 60 to 72 hours. Because of this, warfarin is not fully effective in the initial several days of therapy *(Ansell, 2008 [R])*.

When determining the efficacy and tolerability of warfarin in patients with non-valvular atrial fibrillation, the clinical trials excluded patients using the following criteria:

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

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

(Sebastian, 2000 [R])

Used with permission from Drugs and Aging 2000, Jun:16(6) 409-435.

The clinician will need to balance the potential increase risk in bleeding against the potential decrease risk of thromboembolism when evaluating warfarin therapy.

2. Contraindications

Key Points:

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

Warfarin Allergy or Intolerance

Acute rash, hepatitis, diarrhea or nausea may indicate an allergy or intolerance to warfarin.

Hemorrhage

Anticoagulation with warfarin is contraindicated in patients with active hemorrhage. 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 four to six 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.

Please refer to Appendix A, "Risk Factors for Bleeding during Warfarin Therapy," and Annotation #3, "Adverse Effects," for additional information about predicting the risk of bleeding for individual patients.

Pregnancy

See Annotation #4, "Pregnancy – Contraindicated."

3. Adverse Effects

Key Points:

- The most common adverse effect of warfarin is bleeding. Risk factors for bleeding include patient-related and treatment-related factors.

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 (hematocrit less than 30%), hypertension, heart disease, cerebrovascular disease, renal disease, history of gastrointestinal hemorrhage, active peptic ulcer disease or liver disease, recent or imminent surgery, trauma, excessive alcohol intake, unreliability, frequent or significant falls, regular use of non-steroidal anti-inflammatory (NSAIDs), and use of other medications or natural remedies. In 1998, Beyth, Quinn and Landefeld published a prediction rule for estimation of the risk of bleeding while on outpatient warfarin therapy (see Appendix A, "Risk Factors for Bleeding during 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 to 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 *(Beyth, 1998 [B])*. It is worth noting that both cohorts were derived from patients who were deemed appropriate for outpatient warfarin therapy by their primary physicians. There was no description of the patients who were not enrolled in the trial. 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 *(Landefeld, 1993 [R]; Levine, 2004 [R]; Sebastian, 2000 [R])*. Few, if any, patients with the above noted risk factors have been formally studied.

The Food and Drug Administration (FDA) recently approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35%-50% of the variable dose response to warfarin *(Wood, 2007 [R])*. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs. This issue is discussed further under initiation of warfarin in annotation #7, "Dosing."

Advanced patient age and hypertension are two predictors of risk strongly related to the inherent risk of intracerebral hemorrhage in patients not receiving anticoagulation *(Hart, 1995 [R])*. Combined literature sources support age as a risk for intracerebral hemorrhage that increases by 1.85/year/decade, with particular caution above 75 years of age *(Hart, 1995 [R]; Hart, 1998 [M]; Hart, 2005 [R]*). Retrospective analysis of over 10,000 patients over the age of 65 (men age 77) identified a threefold increased risk (RR 3.0, 95% CI 1.6-6.5) of intracerebral hemorrhage in patients receiving both antiplatelet and warfarin therapy *(Hart, 2005 [R])*.

Treatment-related factors include duration, intensity and variability of warfarin treatment, concomitant use of aspirin, and support patients receive from their providers and home environments. Please refer to

Appendix A, "Risk Factors for Bleeding during Warfarin Therapy," for additional information on bleeding risk in anticoagulation therapy.

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.**

(Fihn, 1996 [B]; Fihn, 1993 [B]; Hylek, 1994 [C]; Landefeld, 1989a [B]; Landefeld, 1989b [C]; Landefeld, 1993 [R]; Launbjerg, 1991 [D]; Levine, 2004 [R]; Palareti, 2000 [C]; Sebastian, 2000 [R])

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. 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 three 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 it is four times as common in women as in men. Skin necrosis has also been reported as a complication occurring in patients with heparin-induced thrombocytopenia (HIT) who are started on warfarin. Because of the extreme rarity of this complication, routine pretesting for this condition in all individuals prior to initiation of oral anticoagulation is not advised *(Beitz, 2002 [R]; Chan, 2000 [R]; Makris, 1996 [D])*.

When warfarin-induced skin necrosis is suspected, patients should be placed on heparin therapy unless there is evidence of HIT. 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 *(Jillela, 1996 [D])*.

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.

(Abdelmalek, 1995 [D]; Ansell, 1993 [R]; Hyman, 1987 [D]; Sallah, 1997 [R]; Talmadge, 2003 [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.

(Caraballo, 1999 [B]; Cornbleet, 1957 [D]; Jamal, 1998 [B]; Kwong, 1978 [D]; Umlas, 1988 [D])

4. Pregnancy – Contraindicated

Warfarin is contraindicated during pregnancy because it crosses the placenta, causing teratogenicity and fetal bleeding. 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 hypocoagulable 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.

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 *(Bates, 2004 [R])*. A study has shown that two pregnant patients with mechanical heart valves had thrombotic complications when treated with LMWH. **Patients with mechanical heart valves who are pregnant are at high risk and should be managed by an anticoagulation expert** *(Robin, 1999 [R])*.

5. Breast-Feeding

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.

6. Monitoring

Test

The International Normalized Ratio (INR) is the preferred test for monitoring warfarin therapy.

The INR is calculated from the Prothrombin Time (PT) as follows:

$$(\text{Patient PT}/\text{Mean Normal PT})^{\text{ISI}}$$

The mean normal PT is the geometric mean of prothrombin times determined from at least 20 fresh samples obtained from healthy men and women. The International Sensitivity Index (ISI) is a measure of sensitivity of the thromboplastin. The manufacturer will frequently provide an ISI specific for the analyzer used. The ISI can be verified by the local laboratory using certified, reference plasmas *(Clinical and Laboratory Standards Institute document H47-A2 One Stage Prothrombin Time [PT] Test and Activated Partial Thromboplastin Time [APTT] Test, 2008 [R])*.

Limitations of INR

There are several recognized limitations of the test, including instrumentation effect on the ISI and erroneous reporting of the ISI by the thromboplastin manufacturer *(Ansell, 2008 [R])*.

Timing and frequency of INR testing

During initiation and maintenance therapy with warfarin, the INR is best measured at least 16 hours after the dose of warfarin.

In most stable patients, INR determinations can be obtained once or twice monthly. No more than six weeks should elapse between determinations *(Ansell, 2008 [R])*.

Influence of Heparin and Lupus Anticoagulants on the INR

Prothrombin reagents contain a heparin neutralizer; however, presence of high concentrations of heparin in plasma samples (e.g., sample collected shortly after IV heparin bolus, or sample collected above an IV infusion of unfractionated heparin, or sample collected through a heparin-coated catheter [central venous line or arterial line]) will spuriously prolong the INR.

Prothrombin reagents contain a high concentration of phosphopholipid; thus, presence of lupus anticoagulants typically does not affect the INR result.

However, there are individual patients in whom lupus anticoagulants may spuriously prolong INR results obtained by some instrument-reagent combinations. In these patients, lupus anticoagulants can cause a prolongation of the PT and INR, resulting in a perceived overestimation of a patient's anticoagulation.

One study suggested that patients with a lupus anticoagulant might require a higher target therapeutic range than patients lacking a lupus anticoagulant; however, recent prospective studies do not confirm superiority of a higher target INR *(Crowther, 2003 [A])*.

Alternatives to INR in Patients with Lupus Anticoagulants

For patients with a prolonged baseline PT/INR due to a lupus anticoagulant, alternatives to the INR have been evaluated. Measurement of chromogenic factor X levels or factor II levels may be helpful in the monitoring of warfarin therapy in selected patients with lupus anticoagulant *(Fairweather, 1998 [R]; Moll, 1997 [D])*. Both the chromogenic factor X and factor II levels may not be readily available.

Blood Samples

Patient samples should be collected in 109 mmol/L (3.2%) sodium citrate when INR testing is performed on anticoagulated plasma *(Adcock, 1997 [B]; Fairweather, 1998 [R])*.

- The volume of sodium citrate in blood tubes used for collection of plasma INR testing should be adjusted when the patient's hematocrit is greater than 55%. Specimens with a high hematocrit will cause spuriously high INR values unless the citrate volume is adjusted *(NCCLS, 2003 [R])*.
- Anticoagulated whole blood may be stored spun or unspun at room temperature for up to 24 hours prior to testing *(Fairweather, 1998 [R])*.

Instruments Including Point of Care Instruments

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. INR values outside of the therapeutic range (2.0-3.0) obtained using a whole blood, fingerstick method may show significant bias when compared to plasma-based INR results obtained on laboratory instruments.

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.

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 *(Ansell, 2008 [R]; Fairweather, 1998 [R])*.

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.

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.

Reagents

Sensitive thromboplastins (ISI values between 0.9 and 1.7) and reagent/instrumentation combinations for which the ISI has been established are recommended for INR testing *(Ansell, 2008 [R])*. 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 *(Fairweather, 1998 [R])*.

7. Dosing

Key Points:

- Patients receiving warfarin for the first time should begin at the patient's estimated average daily dose (typically 5 mg/day; range 2.5-7.5 mg/day), with a recheck of the INR in two to three doses.
- Steady-state INR values will not be realized for up to three weeks following a dose adjustment.

(Nichols-English, 2000 [R])

Testing should be obtained before initiation of warfarin:

- Complete blood count (CBC)
- Platelet count
- PT/INR
- aPTT
- Creatinine
- Liver enzymes (ALT, AST, GGT)
- Albumin

General Principles of Warfarin Dosing

Loading doses 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 supratherapeutic INR and make it more difficult to determine a steady-state dose *(Beyth, 1998 [B]; Crowther, 1999 [A])*.

Studies have 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% at 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 *(Ansell, 2008 [R]; Harrison, 1997 [A]; Hylek, 2001 [B]; Kovacs, 2003 [A])*. 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 *(Crowther, 1999 [A])*. 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 *(Harrison, 1997 [A])*.

The FDA approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35%-50% of the variable dose response to warfarin *(Wood, 2007 [R])*. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs. This issue is discussed further under initiation of warfarin in this annotation.

Patients at high risk for thrombosis, such as those with an active thrombotic process (e.g., VTE) or an underlying malignancy should be initially treated with concomitant immediate-acting anticoagulant (UFH, LMWH, fondaparinux, DTIs) and warfarin therapy. Patients at lower thrombotic risk (e.g., atrial fibrillation without recurrent thromboembolism) can be initiated on warfarin alone.

A single target INR value should be used as a goal endpoint *(White, 1995 [D])*. 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 available in Annotation #8, "Recommended Therapeutic Range for Oral Anticoagulation Therapy." Also, individual disease management guidelines such as ICSI Atrial Fibrillation and ICSI Venous Thromboembolism give specific INR recommendations.

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 Appendix A, "Risk Factors for Bleeding during Warfarin Therapy," for more information on risk factors for bleeding during warfarin therapy.

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.

In most cases, holding warfarin for four 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 #66, "Anticoagulation Bridging."

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 *(Weibert, 2000 [A]; Yacobi, 2000 [A])*. 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.

Prescription and over-the-counter medications can adversely affect the INR response to warfarin. Dietary supplements including 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 Appendices B, "Drug Interactions with Warfarin," and C, "Endogenous Interactions with Warfarin" for more information.

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.

Foods that contain moderate amounts of vitamin K may decrease the INR response to warfarin. Patients should be encouraged to not change their diet while taking warfarin and not change the amount of foods containing vitamin K they normally eat each day. Please refer to Annotation #11, "Key Patient Education Components," for a guide to educating patients regarding warfarin therapy.

Direct thrombin inhibitors (hirudin, argatroban, bivalirudin) and heparins can affect the INR. Please refer to Annotations #36-45, "Direct Thrombin Inhibitors," for more information.

Initiation of Warfarin

Average daily dosing technique (for patients not on heparin)

Average daily dosing technique is useful for patients off UFH and LMWH.

A baseline INR value should be drawn to rule out underlying coagulopathy.

Patients previously taking warfarin can be initiated at the previous dose.

Patients receiving warfarin for the first time should begin at an average dose of 5 mg daily, with a recheck of INR in two to three doses. Lower 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. For patients who weigh more than 80 kg, a higher estimated average initial dose of 7.5 mg may be given. Higher initial dosing nomograms have not shown consistent benefit. Loading doses can increase a patient's risk of supratherapeutic INR and make it more difficult to determine a steady-state dose *(Beyth, 1998 [B]; Crowther, 1999 [A])*.

If the INR is 2.0 or greater after the first three doses, consider decreasing the dose by one-half. Always search for causes of rapid rise in INR such as drug interactions, poor nutritional status, infection, or systemic disease process. See Appendix C, "Endogenous Interactions with Warfarin."

Subsequent INR values are determined at two to three times weekly for one to two weeks, then less often depending on the stability of the INR result.

Steady state anticoagulation occurs between 6 to 12 days. Expect obese patients and patients of advanced age to take longer to reach steady state.

(Ansell, 2008 [R]; Blann, 1999 [D]; O'Connell, 2000 [D])

Flexible daily dosing technique (for inpatients and outpatients on heparin)

The flexible daily dosing technique is useful for patients on concomitant UFH or a LMWH.

A baseline INR value may be drawn to rule out underlying coagulopathy.

Patients are given daily doses of warfarin, adjusted according to the daily INR, until a weekly dose can be determined *(Fennerty, 1984 [D])*.

The dose-response relationship is best interpreted when there are at least 16 hours between dose and laboratory draw.

Use of genomic and clinical prediction rules

The FDA approved updated labeling for warfarin. The agency reports that people with variations in two genes, CYP2C9 and VKORC1, are individually responsible for 35%-50% of the variable dose response to warfarin *(Wood, 2007 [R])*. These genetic variations affect the dose of warfarin that individual patients will need to achieve and maintain therapeutic INRs.

Several studies have demonstrated that these genetic variations do have some influence on the warfarin dose a patient may require *(Caraco, 2007 [A])*. A recent trial used a prediction rule combining genomic testing data with clinical characteristics in predicting a patient's dosing needs. This rule appeared to better predict the eventual weekly dosing needs of patients who required higher or lower doses of warfarin compared to standard dosing techniques such as flexible dosing nomograms or a clinical algorithm. This study does not address the issue of whether a precise initial dose of warfarin translates into improved clinical endpoints, such as a reduction in the time needed to achieve a stable therapeutic INR, fewer INRs that are out of range, and a reduced incidence of bleeding or thromboembolic events. However, this study lays important groundwork for a prospective trial and suggests that such a trial should be powered to detect the benefits of incorporating pharmacogenetic information into the dose algorithm for patients who require high or low doses *(The International Warfarin Pharmacogenetics Consortium, 2009 [B])*.

The work group feels that more clinical trials are necessary before recommending routine testing of patients for these genetic variations. There are many other variables that influence a patient's response to warfarin therapy. Most important is that all patients initiating warfarin need frequent, careful monitoring to assess their response to this therapy.

Maintenance Dosing of Warfarin

An assessment of clinical variables known to affect the INR (including a change of patient adherence, change of other medications [e.g., amiodarone], change of food or alcohol consumption, change of activity level) should be made with each dose adjustment. Always search for the cause of out-of-range values and address them before adjusting the dose.

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.

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

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.

If two consecutive weekly INR values are within range and there has not been a change in clinical variables known to effect the INR, the interval between draws may be gradually increased to monthly, and not more than six weeks.

Options for dosing management

Anticoagulation clinics have been shown to significantly reduce patients' risks of adverse events.

Though traditionally warfarin has been monitored at a central laboratory and managed by the patient's physician, new monitoring and management options have emerged.

Anticoagulation clinics staffed by pharmacists and registered nurses have been shown to significantly reduce patients' risks of adverse events. There are published "before and after" design trials comparing patients whose warfarin was managed by their personal physicians with patients whose warfarin was managed by anticoagulation clinics *(Chiquette, 1998 [C]; Cortelazzo, 1993 [D]; Garabedian-Ruffalo, 1985 [D]; Wilt, 1995 [D])*. All five trials reported reductions in the incidence of major hemorrhage and thromboembolism. Beyth, et al., published a randomized control trial of 325 patients 65 years of age and older that compared patients whose warfarin was managed by their personal physicians with patients whose was warfarin managed by anticoagulation clinics *(Beyth, 2000 [B]; Chiquette, 1998 [C]; Cortelazzo, 1993 [D]; Garabedian-Ruffalo, 1985 [D]; Wilt, 1995 [D])*. See the Support for Implementation section under Resources Available for more resources for the development and support of anticoagulation clinics.

Computer-assisted dosing has been slow to develop, but may someday improve the quality of anticoagulation adjustments and offer superior management for difficult or high-risk patients *(Beyth, 2005 [R]; Menendez-Jandula, 2005 [A])*.

Selected point-of-care instruments have received FDA approval for patient self-testing.

While some patients may prefer self-management, clinical experience, reimbursement and research are insufficient to support widespread implementation of patient self-management. Further research is needed to better identify appropriate candidates for self-management and to delineate the key components of education and support.

8. Recommended Therapeutic Range for Oral Anticoagulation Therapy

Indication	Target INR (Range)
Mechanical prosthetic valves (high risk)	3.0 (2.5 – 3.5)
Bileaflet mechanical valve in aortic position	2.5 (2.0 – 3.0)
Tissue valve	2.5 (2.0 – 3.0)
Valvular (rheumatic) heart disease	2.5 (2.0 – 3.0)
Atrial fibrillation	Greater than or equal to 2.0 for 4 consecutive weeks prior to cardioversion and anticoagulation 2.0-3.0 for 8 weeks following cardioversion
Venous thromboembolism treatment – deep vein thrombosis/pulmonary embolism	See ICSI Venous Thomboembolism Diagnosis and Treatment guideline.
Venous thromboembolism prophylaxis	See ICSI Venous Thomboembolism Prophylaxis guideline.

(Hirsh, 2008 [R])

For specific treatment recommendations, please see the ICSI Atrial Fibrillation guideline, the ICSI Venous Thromboembolism Diagnosis and Treatment guideline or the Venous Thromboembolism Prophylaxis guideline.

9. 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.

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.

(Ansell, 2008 [A]; Butler, 1998 [R]; Crowther, 2000 [A]; Reigert-Johnson, 2002 [D]; Shields, 2001 [B]; Whitling, 1998 [C])

Important Considerations for Vitamin K Dosing

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

In a hospital setting, when patients are ill or taking nothing by mouth, 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.

Administration of vitamin K by subcutaneous or intramuscular injections are not recommended due to unpredictable absorption, which can lead to erractic correction of INR and resistance to warfarin *(Ansell, 2008 [R]; Shields, 2001 [B]; Whitling, 1998 [C])*.

Table 2: Correction of Supratherapueutic Anticoagulation Caused by Warfarin

Correction of Supratherapeutic INR Caused by Warfarin			
Bleeding Severity	INR *	Warfarin/FFP	Vitamin K (Do not expect reversal for at least 16-24 hrs)
No significant bleeding	< 5.0	Decrease or omit dose	NA
	5.0-8.9	Omit 1-2 doses and decrease dose If bleeding risk is high, omit 1 dose and give vitamin K	1-2.5 mg by mouth If rapid reversal is required because of urgent surgery, may give ≤ 5 mg by mouth If INR is still high, can give additional 1-2 mg by mouth
	≥ 9.0	Hold, give vitamin K and decrease dose	2.5-5 mg by mouth
Serious bleeding at any elevation of INR	NA	Hold, give vitamin K and supplement with FFP **, PCC or rVIIa	10 mg IV by slow infusion; may repeat every 12 hrs
Life-threatening bleeding	NA	Hold, give vitamin K and supplement with FFP**, PCC or rVIIa	10 mg IV by slow infusion; repeat if necessary depending on INR

FFP = fresh frozen plasma PCC = prothrombin complex concentrate rVIIa = recombinant factor VIIa

Vit K_1 available as 5 mg tab, IV solution

* If INR > 5, recommend recheck every 24 hours until stabilized.

** FFP units average 250-275 mL. Administer 15 cc/kg FFP, round to the nearest unit.

Adapted with permission from: Ansell, Jack; *Chest* 2008; 133:160-198 DOI 10.1378/chest.08-0670, Pharmacology and Management of the Vitamin K Antagonists: ACCP Evidence-Based Clinical Practice Guidelines (8th edition)

10. Combined Warfarin and Antiplatelet Therapy

In general, it is not recommended that antiplatelet medications (e.g., aspirin, clopidogrel) be added to warfarin therapy unless there is a strong need for both therapies. Combined use of these agents has been shown to increase bleed risk two- to threefold. Patients with risk factors for atherosclerotic cardiovascular disease (e.g., diabetes, hypertension) and those with chronic stable atherosclerotic cardiovascular disease can usually be started on warfarin with the discontinuation of the antiplatelet therapy.

Circumstances that may necessitate the combined use of antiplatelets and warfarin may include acute coronary syndrome or high-risk valve patients. However, even in these circumstances, the patient's individual bleeding risk should be taken into account. If bleed risk is prohibitive with combined use, one could consider discontinuing warfarin or decreasing the target INR in order to lower that patient's risks.

Consultation with an anticoagulation expert may be helpful in determining the risks and benefits of combined warfarin and antiplatelet use.

(Dentali, 2007 [M]; Hart, 2005 [R]; Madhwal, 2008 [R])

11. Key Patient Education Components

Mechanism of action of warfarin: it depletes certain coagulation factor proteins in the blood.

Time of day to take warfarin: it should be taken at approximately the same time each day. 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.

Explanation of INR, target range and regular testing.

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

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

Need to inform all health care providers of anticoagulation therapy, especially if potentially undergoing an invasive procedure, surgery or dental work.

Drug interactions:

- What to do if a new medication is initiated or a medication is discontinued, especially if the interaction with warfarin is unknown: check INR within three to four days.
- Drugs that affect the absorption of warfarin.
- Drugs that increase or decrease the effect of warfarin.
- 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.

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.

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

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

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

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

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

MedicAlert® bracelet/necklace and warfarin ID card.

Please refer to Appendix D, "Patient Education Guide to Warfarin Therapy," for a guide to patient education regarding warfarin therapy.

Heparin (Unfractionated and Low-Molecular-Weight)

12. Introduction

Heparin's (UFH, LMWH) anticoagulant effect is due to the presence of a pentasaccharide sequence, which potentiates the action of antithrombin 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.

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.

LMWHs are depolymerized by-products of UFH. Pharmacological advantages of LMWH relate to superior absorption and consistent dose effect response.

13. Contraindications

- Active major bleeding, including intracerebral hemorrhage within past two weeks, subarachnoid hemorrhage until definitively treated.
- Thrombolytics given within past 24 hours for acute stroke.
- Hypersensitivity to heparin or pork products.
- Heparin-induced thrombocytopenia (HIT). Patients with a history of HIT who require cardiac surgery may receive unfractionated heparin for the procedure if they are antibody negative for platelet factor 4, (PF4). Alternate anticoagulants should be used for preoperative and postoperative anticoagulation *(Warkentin, 2007b [R])*.
- Renal failure creatinine clearance of < 30 ml/minute (LMWH and fondaparinux).

14. Precautions

Active or recent history of gastrointestinal ulceration and hemorrhage.

Bacterial endocarditis.

Bleeding diathesis.

Concomitant therapy with agents that inhibit platelets.

Congenital or acquired bleeding disorders.

Hemorrhagic stroke.

Status post brain, spinal or ophthalmologic surgery.

Uncontrolled arterial hypertension.

Diabetic retinopathy.

15. Adverse Effects

Key Points:

- Heparin-induced thrombocytopenia (HIT) should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater then 50% decrease in platelet count from baseline labs while on heparin. In post-surgical patients, HIT should be suspected when the platelet count falls 50% from the post-operative platelet count peak *(Warkentin, 2007 [R])*.
- All heparin should be stopped in patients suspected of having HIT until antibody test results are available.

- If the patient is on concomitant warfarin and heparin-induced thrombocytopenia is suspected, the warfarin should be stopped, the warfarin effects corrected, and the patient started on DTI therapy.

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.

The rate of major bleeding associated with 5-10 days of IV unfractionated heparin in patients with acute venous thromboembolism (VTE) is 0%-7.0% and the rate of fatal bleeding 0%-2.0%. The rate of major bleeding associated with 5-10 days of subcutaneous 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 *(Campbell, 1996 [A]; Hirsh, 2004 [R]; Hull, 1990 [A]; Levine, 2004 [R])*.

Heparin-Induced Thrombocytopenia (HIT)

HIT is an immune-mediated reaction to heparins. It occurs in 2%-3% of patients treated with UFH and less than 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 *(Warkentin, 2003 [R])*.

HIT should be suspected in patients who develop a skin lesion reaction at the injection site, have a systemic reaction to a bolus administration of heparin, or develop a greater than 50% decrease in platelet count from baseline labs while on heparin. In post-surgical patients, HIT should be suspected when the platelet count falls 50% from the post-operative platelet count peak *(Warkentin, 2007 [R])*.

Delayed-onset HIT is an increasingly recognized form of this disorder. Patients with delayed-onset HIT typically present with thromboembolic complications one to two weeks (studies show the entire range 5 to 40 days) after receiving their last dose of LMWH or UFH. They frequently display mild or moderate thrombocytopenia. When HIT is not recognized as the etiology of the thromboembolic complication, the patient is frequently rechallenged with heparin, causing significant worsening of the thrombosis, as well as the thrombocytopenia. These patients typically have very high titers of HIT-related antibodies. The possibility of delayed onset HIT should be considered in any patient presenting with thromboembolism after a recent hospitalization.

Although fondaparinux therapy can result in anti-PF4/heparin antibodies, they usually do not result in platelet activation. Rare cases of HIT related to fondaparinux therapy have been reported *(Rota, 2008 [D]; Warkentin, 2008 [D]; Warkentin, 2007 [D])*.

Patients suspected of having any form of HIT should have their heparin stopped while antibody testing for HIT is performed. Patients with a high clinical probability of having HIT should be treated with an appropriate alternative anticoagulant before antibody test results are available. Direct thrombin inhibitors (DTIs) are the alternative anticoagulant of choice for patients with HIT. Three brands are FDA approved: argatroban, lepirudin (Refludan®), and most recently, bivalirudin (Angiomax®) *(Warkentin, 2003 [R]; Warkentin, 2004a [R]; Warkentin, 2004b [R])*.

If a patient is receiving warfarin when there is a high clinical probability of HIT, the warfarin should be stopped. The warfarin effect should be reversed with vitamin K, and DTI therapy should be initiated. Studies have demonstrated that the manufacturer recommended dosages for argatroban and lipirudin are too high. Therefore, lower doses are recommended (see Annotation #43, "Dosing.") Low maintenance doses of

warfarin can be restarted during DTI therapy after the platelet count has significantly improved and there is clinical improvement in the patient's thrombosis. There should be at least a five-day overlap of the DTIs and warfarin. The DTI therapy should be continued until the platelet count stabilizes *(Warkentin, 2004b [R])*.

Please refer to Annotations #36-45, "Direct Thrombin Inhibitors," for more information.

16. Pregnancy

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 *(Bates, 2004 [R])*.

Patients with mechanical heart valves who are pregnant are at high risk and should be managed by an anticoagulation expert. A 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, the available data sets, clinical trials, reviews and registry data suggest that, compared with UFH, LMWHs may be safe and effective agents in pregnant women with mechanical heart valves *(Seshadri, 2005 [M])*.

The ACCP recommends that women requiring long-term anticoagulation with warfarin who are attempting pregnancy be monitored with frequent pregnancy tests. They recommend substituting UFH or a LMWH for warfarin when pregnancy is achieved *(Bates, 2004 [R])*. LMWHs cause less HIT and bone loss during pregnancy than UFH.

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

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

17. Breast-Feeding

Heparin is not secreted in breast milk and can be given safely to nursing mothers *(Bates, 2004 [R])*.

Unfractionated Heparin (UFH)

18. Monitoring

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. The aPTT therapeutic range should correspond to a plasma heparin concentration of 0.3 to 0.7 units/mL by an anti-Xa inhibition assay (0.2 to 0.4 units/mL by protamine titration assay) *(Brill-Edwards, 1993 [R])*.

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-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 units unfractionated heparin in 24 hours), when the pretreatment aPTT is prolonged or when a lupus anticoagulant has been previously documented in the patient *(Hirsh, 2004 [R]; Olson, 1998 [R])*.

Patients receiving UFH or a LMWH should be monitored for heparin-induced thrombocytopenia (HIT). A platelet count of less than 50% of baseline or the postoperative peak during heparin therapy may indicate the development of HIT. The recommended frequency of monitoring is dependent upon the patient's risk of developing HIT. Postoperative patients receiving prophylactic or therapeutic UFH have the highest risk of HIT requiring platelet monitoring every other day from day 4 to 14 or until the heparin is discontinued. Any patient receiving therapeutic UFH, medical and obstetrical patients receiving prophylactic UFH, medical and obstetrical patients receiving LMWH after a dose of UFH, postoperative patients receiving prophylactic LMWH and postoperative/critical care patients receiving UFH flushes are at lower risk for developing HIT, but still warrant every-other-day platelet count monitoring between day 4 and 14 or until the heparin is discontinued.

Medical and obstetrical patients receiving LMWH, medical patients receiving UFH flushes and patients receiving therapeutic or prophylactic fondaparinux are at very low risk of developing HIT and routine platelet count monitoring is not needed. Patients receiving outpatient heparin therapy should be instructed to seek immediate medical attention if the signs or symptoms of HIT develop.

Patients who have been exposed to heparin within the past 100 days and patients with unclear heparin exposure histories should undergo baseline platelet count testing with repeat platelet count testing within 24 hours of the first heparin dose to evaluate the possibility of rapid onset HIT.

See Annotation #15, "Adverse Effects," for more information.

(Hirsh, 2008 [R])

19. Dosing

Testing should be obtained before initiation of UFH:

- Complete blood count (CBC)/Platelet count
- PT/INR
- APTT
- Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

- Liver enzymes (ALT, AST, GGT)
- Albumin

Dosing – Prophylactic

See ICSI Venous Thomboembolism Prophylaxis guideline and ICSI Venous Thomboembolism Prophylaxis for the Medically Ill Patient order set.

Dosing – Therapeutic

Weight-based, institution-specific nomograms are strongly recommended for patients on therapeutic intravenous UFH. 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 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, 1991 [B]; Raschke, 1993 [A])*. Each institution must develop its own nomograms based upon their unique specific therapeutic ranges. Please refer to Appendix E, "Example of a Heparin Nomogram," for an example of a heparin nomogram.

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 agent's package insert or their institutional protocols for the specific agent's heparin protocol.

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.

Also, draw hemoglobin/hematocrit, platelet count, activated partial thromboplastin time (aPTT) and prothrombin time (PT) before administering UFH.

Initiation of UFH

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 evolving. Please refer to the ICSI Diagnosis and Initial Treatment of Ischemic Stroke guideline. Note the time of initial heparin bolus.

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

Maintenance

Obtain an aPTT level or heparin assay six hours after the initiation of IV heparin drip. Adjust the IV drip according to institutional protocols.

20. Correction of Supratherapeutic Anticoagulation Caused by Unfractionated Heparin

Protamine sulfate administered by slow IV infusion over 10 minutes reverses the anticoagulation effects of unfractionated heparin.

$$\frac{\text{Bolus dose of UFH (units) divided by 100 = protamine dose}}{\text{Hourly infusion rate of UFH (units) divided by 40 = protamine dose}}$$

Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension.

(Hirsh, 2004 [R])

21. Key Patient Education Components

Importance of understanding heparin assays, INRs and target ranges.

Know and watch for signs of bleeding.

Low-Molecular-Weight Heparin (LMWH)

22. Monitoring

Patients receiving LMWH are at lower risk of developing HIT than patients receiving UFH. The need for platelet count monitoring during LMWH therapy depends on the indication for anticoagulation. Postoperative patients receiving LMWH and medical/obstetrical patients receiving LMWH following at least one dose of UFH (including UFH IV flushes) within the past 100 days infrequently experience HIT. Therefore, a baseline platelet count followed by platelet counts every two to three days is recommended until the LMWH is discontinued or until day 14 of therapy, whichever comes first.

Medical and obstetrical patients receiving only LMWH rarely develop HIT. After a baseline platelet count, routine platelet count monitoring is not required. If there is clinical uncertainty about whether the patient may have received UFH, community standard is to monitor platelet counts monthly.

All patients receiving any form of heparin should be instructed to immediately seek medical attention if signs or symptoms of venous thromboembolism are suspected *(Warkentin, 2004a [R])*.

23. Dosing

Testing should be obtained before initiation of LMWH:

Complete blood count (CBC)/Platelet count

PT/INR

aPTT

Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

Liver enzymes (ALT, AST, GGT)

Albumin

LMWH should not be administered by intramuscular injection.

Therapeutic doses of a LMWH are different from prophylactic doses.

Doses of different LMWHs are not interchangeable *(Burnett, 1998 [R]; Frydman, 1996 [R]; Weitz, 1997 [R])*.

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

The dose should be modified for patients with impaired renal function. It may be necessary to monitor the anti-Xa level in these patients. LMWHs are relatively contraindicated in patients with a creatinine clearance less than 30 or who are receiving dialysis. 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:

$$\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{weight in kg} \times 0.85}{(72 \times \text{serum creatinine})}$$

The optimal dose of LMWH has not been established in patients with low body weight (less than 50 kg) (possibly higher than usual dose), obesity (possibly lower than usual dose), or pregnancy (changing dose due to changing creatinine clearance). It may be necessary to monitor the anti-Xa level in these patients *(Gerlach, 2000 [D])*.

Table 3: Therapeutic Dosing of LMWH

FDA-Approved Indications	Enoxaparin	Dalteparin	Tinzaparin
DVT and/or pulmonary embolism (PE)	1 mg/kg every 12 hours for 5 days or more with transition to warfarin; FDA approved for both inpatient and outpatient use 1.5 mg/kg daily for 5 days or more with transition to warfarin; FDA approved for inpatient use only	100 units/kg subQ every 12 hours for 5 days or more with transition to warfarin; Not FDA approved for venous thromboembolism treatment	175 anti-Xa units/kg daily for 6 days or more with transition to warfarin
Unstable angina/ non-Q-wave MI	1 mg/kg every 12 hours plus aspirin (100-325 mg) for 2-8 days	120 units/kg every 12 hours plus aspirin for 5-8 days.	Not FDA approved
Severe renal impairment (creatinine clearance less than 30 mL/min)	1 mg/kg ONCE daily	Recommend reduced dose. Manufacturer recommended dose is not available.	Recommend reduced dose. Manufacturer recommended dose is not available
Extended treatment of symptomatic VTE in cancer patients	Not FDA approved	First 30 days: 200 units/kg subQ every 24 hrs Months 2-6: 150 units/kg subQ every 24 hrs	Not FDA approved
Acute STEMI managed medically or with subsequent PCI	< 75 years old: 30 mg single IV bolus + 1 mg/kg subQ dose followed by 1 mg/kg subQ every 12 hrs + aspirin ≥ 75 years old: 0.75 mg/kg subQ every 12 hrs (no bolus)	Not FDA approved	Not FDA approved
Notes			May interfere with PT/INR

Please see the ICSI Venous Thromboembolism Diagnosis and Treatment guideline and the ICSI Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS) guideline for more information.

(Merli, 2001 [A])

Table 4: Prophylactic Dosing of LMWH

FDA-Approved Indications	Enoxaparin	Dalteparin	Tinzaparin
Hip fracture surgery	5,000 units subQ every 24 hrs beginning 12-24 hrs postop + mechanical prophylaxis If surgery is delayed, initiate between admission and surgery.	30 mg subQ every 12 hrs beginning 12 hrs postop + mechanical If surgery is delayed, initiate between admission and surgery.	Not FDA approved
Hip replacement	30 mg every 12 hours beginning 12 hours postop and every 12 hours for minimum 10 days (consider extending prophylaxis to 28-35 postop or 40 mg every 24 hours beginning 9-15 hours preop for minimum 10 days (consider extending prophylaxis to 28-35 days postop)	2,500 units 2-8 before surgery and then 5,000 units every 24 hours postop for minimum 10 days (consider extending prophylaxis to 28-35 postop) or 5,000 units 10-14 hours before surgery and then every 24 hours postop for minimum 10 days (consider extending prophylaxis to 28-35 postop)	Not FDA approved
Knee replacement	30 mg every 12 hours beginning 12 hours postop for a minimum of 10 days postop	2,500 units 2-8 hours before surgery and then 5,000 units every 24 hours postop for minimum 10 days postop or 5,000 units 10-14 hours before surgery and then every 24 hours postop for minimum 10 days postop Not FDA approved	Not FDA approved
Abdominal surgery (general surgery)	40 mg 2 hours before surgery and then every 24 hours until discharge	2,500-5,000 units 1-2 hours before surgery and then every 24 hours until discharge.	Not FDA approved
Severe renal impairment (creatinine clearance less than 30 mL/min)	30 mg every 24 hr	Recommend reduced dose. Manufacturer recommended dose is not available.	Recommend reduced dose. Manufacturer recommended dose is not available.
Severely obese patients (BMI 35 or more)	Increase dose by 25%	Increase dose by 25%	Recommend increased dose. Manufacturer recommended dose is not available.
Medical patients during acute illness	40 mg subQ every 24 hrs	5,000 units subQ every 24 hrs	Not FDA approved

Standard practice in the U.S. is dosing dalteparin starting postop.

Please refer to the ICSI Venous Thromboembolism Prophylaxis guideline for more information.

24. Correction of Supratherapeutic Anticoagulation Caused by LMWH

No agent, including fresh frozen plasma (FFP) and vitamin K, is effective for complete reversal of supratherapeutic anticoagulation with LMWH. Reversal of LMWH with protamine sulfate is incomplete, with neutralization of 60%-75% at most. However, protamine should be considered for patients with severe life-threatening bleeding. Anaphylaxis occurs in 1% of patients who have previously received protamine (such as NPH insulin). Other adverse effects include hypotension *(Hirsh, 2004 [R])*.

Administering protamine slowly can minimize adverse reactions to protamine, such as hypotension or bradycardia *(Hirsh, 2004 [R])*. Note: Excessive protamine doses may worsen bleeding potential *(Lacy, 2008 [R])*.

If LMWH has been administered within the last eight hours (unlabeled use):

Enoxaparin

- First dose: 1 mg protamine for each 1 mg of enoxaparin. Administered by slow IV infusion over 10 minutes *(Trissel, 2005 [R])*
- Second dose: 0.5 mg protamine for each 1 mg enoxaparin. Administered by slow IV infusion over 10 minutes. Do not exceed 50 mg in 10 minutes *(Trissel, 2005 [R])*

Dalteparin and Tinzaparin

First dose: 1 mg protamine for each 100 anti-Xa units of dalteparin or tinzaparin Administered by slow IV infusion over 10 minutes. Do not exceed 50 mg in any 10 minutes *(Trissel, 2005 [R])*.

Smaller doses are needed if the LMWH was administered more than eight hours ago.

25. Key Patient Education Components

Over-the-counter and prescription drugs that should not be taken while on LMWH.

Importance of understanding heparin assays, INRs and target ranges.

Know and watch for signs of bleeding.

Proper technique for injecting LMWH.

Restrictions for other conditions including deep vein thrombosis, stroke or stable coronary artery disease. Please refer to related ICSI guidelines for more information.

Importance of adhering to prescribed regimen.

Tables of patient education resources, along with patient and provider-oriented Web sites, are attached in the Support for Implementation section.

Synthetic Pentasaccharide (Fondaparinux)

26. Introduction

Fondaparinux is a synthetic compound composed of the essential pentasaccharide sequence that selectively inhibits factor Xa.

27. Contraindications

Active major bleeding including intracerebral hemorrhage within past two weeks, subarachnoid hemorrhage until definitively treated.

Bacterial endocarditis.

Severe renal impairment defined by CrCl (Cockroft-Gault) < 30 mL/minute.

Secondary increased risk for major bleeding episodes (ARIXTRA product information, 2008).

Thrombolytics given within past 24 hours for acute stroke.

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.

28. Precautions

Fondaparinux should be administered according to recommended regimen especially with respect to timing of the first dose after surgery.

In hip fracture, hip replacement, knee replacement or abdominal surgery, clinical studies show that the administration of fondaparinux before six hours after surgery has been associated with increased risk of major bleeding.

Precautions:

- Active or history of recent gastrointestinal ulceration and hemorrhage.
- Bleeding diathesis.
- Concomitant therapy with agents that inhibit platelets.
- Congenital or acquired bleeding disorders.
- Hemorrhagic stroke.
- Status recent post brain, spinal or ophthalmologic surgery.
- Uncontrolled arterial hypertension.
- Diabetic retinopathy.
- Needle guard of the prefilled syringe contains dry natural latex rubber; it is possible but not necessary for the administration that the needle guard may come in contact with the patient and pose an allergy risk.

29. Adverse Effects

Anemia has been reported in some patients receiving fondaparinux. Asymptomatic elevation in AST and ALT associated with an increase in bilirubin can occur in a small percentage of patients.

30. Pregnancy

The safety of fondaparinux in pregnant women is unknown. Limited clinical experience suggests that fondaparinux may cross the placental barrier, resulting in low but measurable anti-Xa activity in the umbilical cord *(Weitz, 2004 [R])*.

Studies performed in pregnant rats and rabbits have not shown impairment of fertility or a teratogenic effect on the fetus, resulting in the drug being classified as "class B." Only a few case reports of use during pregnancy have published in the scientific literature *(Gerhardt, 2007 [D]; Harenberg, 2007 [D]; Mazzolai, 2006 [D])*. Safety of the drug in nursing women has also not been studied to date although, again, in lactating rats, only a small amount was found in breast milk.

31. Breast-Feeding

Animal studies have shown secretion of fondaparinux in breast milk. It is unknown if humans secrete fondaparinux in breast milk.

32. Monitoring

The heparin assay (anti-Xa) has been used to monitor effects of fondaparinux; however, in most clinical situations, monitoring may not be necessary. Indications for monitoring of fondaparinux include patients weighing over 180 kg or those in whom the level of anticoagulation needs to be checked prior to a procedure. There is limited data on use of fondaparinux in pregnancy, but it is listed under category B.

A platelet count should be obtained prior to the initiation of fondaparinux. Antibodies to fondaparinux rarely interact with platelet factor 4. There are rare reports of HIT associated with fondaparinux *(Warkentin, 2007 [D])*. Fondaparinux is not recommended for patients with platelets less than 100,000 mm_3 due to the overall increased risk of bleeding.

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 Venous Thromboembolism Prophylaxis guideline.

33. Dosing

Testing should be obtained before initiation of fondaparinux:

- Complete blood count (CBC)/Platelet count
- PT/INR
- aPTT
- Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

- Liver enzymes (ALT, AST, GGT)
- Albumin

Therapeutic doses are different than prophylactic dosing.

Fondaparinux is not recommended for patients with platelets less than 100,000 mm_3.

The dose of fondaparinux should be modified in patients with renal impairment. Fondaparinux is contraindicated in patients with a creatinine clearance less than 30 mL/min. Fondaparinux should not be used in patients who are receiving dialysis.

The optimal dose of fondaparinux has not been established in patients with obesity (possibly lower than usual dose). It may be necessary to monitor the anti-Xa level in these patients *(Gerlach, 2000 [D])*.

There is limited data on use of fondaparinux in pregnancy.

Table 5: FDA Approval Status, Indications and Dosing of Fondaparinux

FDA-Approved Indication (Adult)	Fondaparinux
Hip-fracture surgery, hip/knee replacement surgery, abdominal surgery	2.5 mg subcutaneous every 24 hrs
Therapy for deep vein thrombosis including pulmonary embolism	Less than 50 kg, 5.0 mg subcutaneously every 24 hrs 50-100 kg, 7.5 mg subcutaneously every 24 hrs More than 100 kg, 10 mg subcutaneously every 24 hrs

(Bauer, 2001 [A]; Bounameaux, 2002 [M]; Eriksson, 2001 [A]; Lassen, 2002 [A]; Turpie, 2002 [A])

Please refer to the ICSI Venous Thromboembolism Diagnosis and Treatment and Venous Thromoembolism Prophylaxis guidelines for more information.

34. Correction of Supratherapeutic Anticoagulation Caused by Fondaparinux

There is no antidote for excessive bleeding due to fondaparinux. Recombinate factor VIIa (rFVIIa) has shown promise as a possible antidote in studies utilizing healthy volunteers. rFVIIa treatment can be complicated by thrombosis. Up to 7% of patients with acute intracerebral hemorrhage who received rFVIIa therapy experienced an adverse thromboembolic event *(Crowther, 2008 [R]; Mayer, 2007 [A])*. Enzymes capable of degrading heparin have also been investigated as a future treatment for excessive bleeding due to fondaparinux.

(Bijsterveld, 2002 [A]; Warkentin, 2002 [R]; Weitz, 2004 [R]; Yu, 2000 [NA])

35. Key Patient Education Components

Importance of understanding fondaparinux.

Know and watch for signs of bleeding.

Proper technique for injecting fondaparinux.

Restrictions for other conditions including deep vein thrombosis, stroke or coronary artery disease. Please refer to related ICSI guidelines for more information.

Importance of adhering to prescribed regimen.

Direct Thrombin Inhibitors

36. Introduction

Direct thrombin inhibitors (DTIs) – argatroban, bivalirudin, lepirudin – are a relatively new class of anticoagulant drugs. They exert their anticoagulant effect by directly attaching to and inhibiting 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.

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.

37. Contraindications

- Active major bleeding
- Hypersensitivity to hirudin, lepirudin, bivalirudin, argatroban

38. Precautions

- Severe hypertension
- History of recent major surgery
- History of recent major bleeding
- History of recent cerebrovascular accident
- Liver dysfunction (argatroban)
- Renal dysfunction (lepirudin)
- gastrointestinal ulceration
- Patients with repeat courses of lepirudin may require more frequent monitoring due to antibody formation
- Rare case reports of anaphylaxis with reexposure to lepirudin

39. Adverse Effects

- Hemorrhage
- Patients with repeat courses of lepirudin may require more frequent monitoring due to antibody formation.

40. Pregnancy

- Unknown

41. Breast-Feeding

- Unknown

Types of Direct Thrombin Inhibitors

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.

Bivalirudin (Angiomax®)

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

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 subcutaneous dose. It has almost irreversible binding to thrombin and has been associated with an increased risk of major bleeds in one study.

42. Monitoring

- The aPTT testing is commonly used to monitor DTIs.
- The ecarin clotting time has been shown to be a **superior test** for monitoring recombinant hirudin therapy. However, these tests are not yet widely available in clinical laboratories.

43. Dosing

Testing should be obtained before initiation of direct thrombin inhibitors:

Complete blood count (CBC)/Platelet count

PT/INR

aPTT

Creatinine

Obtain if there is clinical suspicion of abnormal results based on patient history and physical:

Liver enzymes (ALT, AST, GGT)

Albumin

- **Argatroban (Acova®)**

  Argatroban has a short half-life (less than 1 hour) and is dosed at 2 mcg/kg/min with adjustments to maintain aPTT at 1.5-3.0 times normal (not to exceed 100 seconds).

  Patients with heart failure, multiple organ system failure and anasarca, as well as those in the immediate post-cardiac surgery period, should receive an initial infusion rate between 0.5 and 1.2 mcg/kg/min monitored using the APTT *(Warkentin, 2008a [R])*.

- **Bivalirudin (Angiomax®)**

  Bivalirudin is dosed as a 0.75 mg/kg bolus dose, followed by a continuous infusion of 1.75 mg/kg/hr for the duration of the percutaneous coronary intervention (PCI) procedure. Continuation of bivalirudin infusion following PCI for up to four hours post-procedure is optional, at the discretion of the treating physician. After four hours, an additional IV infusion of bivalirudin may be initiated at a rate of 0.2 mg/kg/hr for up to 20 hours if needed.

- **Lepirudin (recombinant hirudin) (Refludan®)**

  The drug is dosed at 0.4 mg/kg bolus IV, followed by 0.15 mg/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.

  Patients receiving lepirudin in the setting of HIT should receive a lower dose of drug to decrease the risk of major bleeding. Patients with a serum creatinine of < 1 mg/dL should receive an infusion rate of no more than 0.10 mg/kg/h. Patients with a serum creatinine between 1 mg/dl and 1.6 mg/dl should

have their infusion rate decreased to 0.05 mg/kg/h. The infusion rate should be decreased further for patients with higher serum creatinine levels.

The bolus should be omitted. If there is severe thrombosis threatening life or limb, a reduced bolus of 0.2 mg/kg can be given. APTT monitoring should be performed every four hours until steady state is achieved. The target APTT range is 1.5 to 2 times the patient's baseline or the laboratory's mean APTT *(Warkentin, 2008a [R])*.

44. Correction of Supratherapeutic Anticoagulation Caused by Direct Thrombin Inhibitors

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.

(Hirsh, 2004 [R]; Weitz, 2004 [R])

45. Key Patient Education Components

Importance of understanding aPTT and target ranges.

Know and watch for signs of bleeding.

Antiplatelet Agents

46. Introduction

Platelet involvement with pathologic thrombosis and vascular occlusion in both venous and arterial systems has been a recognized target and challenge for therapeutic intervention. Antiplatelet drugs provide relatively safe and variably efficacious alternatives for reduction of excessive risk in several common clinical conditions, notably cardiac and cerebral atherothrombosis. In modern clinical practice, antiplatelet drugs play a role with other means of risk reduction in both primary and secondary prevention of vascular morbidity, and in selected acute event-management situations. There is substantial basic scientific and clinical trial data available to make rational and selective management decisions for individual patients in all conceivable settings of clinical practice.

Principles:

1. Antithrombotic therapeutic benefit is relative to individual patient morbidity, tolerance and hemorrhagic risk.
2. In general, individual patient thrombotic risk must exceed 3% per year to realize a clinically meaningful benefit from antiplatelet drugs.

For specific treatment recommendations, please see the related ICSI guidelines.

Oral Agents

- **Aspirin**

  Thoroughly evaluated for over 30 years as an antiplatelet drug, aspirin has been confidently determined to prevent vascular death by 15%, and to prevent non-fatal vascular events by about 30%, based on meta-analysis of over 100 randomized trials *(Antithrombotic Trialists, 2002 [M])*. The whole spectrum of atherosclerosis has been evaluated, from low-risk apparently healthy individuals to those with acute

stroke and myocardial infarction, with observation intervals from a few weeks to several years. Both absolute benefits and the size of proportional effects are heterogeneous in different clinical settings.

Its antithrombotic effect derives from the permanent inactivation of cyclooxygenase-1, or COX-1, expressed in megakaryocytes and platelets. This enzyme begins prostanoid biosynthesis resulting in several prostaglandins, including particularly thromboxane-A2, which activates platelets with adhesion to (damaged) vascular intima and release of other cytokines, resulting in local thrombus formation. Since only 10% of the platelet pool is replenished each day, once-daily dosing is adequate to maintain virtually complete inhibition of prostaglandin-mediated activation of platelet thrombogenic processes.

Its somewhat dissimilar effect on the isomer COX-2, expressed in many tissues but particularly monocytes, constitutes its anti-inflammatory benefits. There is approximately 100-fold greater dose requirement for anti-inflammatory as antithrombotic effects of aspirin.

Aspirin is rapidly absorbed in the stomach and upper intestine, and inhibition of platelet function is evident within one hour. This process is significantly slowed by enteric coating of tablets.

- **Clopidogrel**

  Clopidogrel a thienopyridine that selectively blocks epinephrine-induced platelet aggregation. It has no effect on prostaglandin metabolism. It is rapidly absorbed after ingestion and extensively metabolized, with clinical antiplatelet effects due to a short-lived metabolite.

  Recovery of platelet function after drug discontinuation requires about seven days, paralleling the dynamic of platelet turnover, suggesting that as with aspirin, the active CPG metabolite permanently affects platelet protein, which cannot be repaired within the platelet lifespan.

- **Dipyridamole**

  Antiplatelet effects are due to multiple mechanisms of action, including accumulation of platelet cyclic AMP by several enzymatic interactions. Dipyridamole produces vasodilation by parallel actions on non-platelet systems. Erratic absorption has been a practical problem of conventional preparations, with the current modified-release formulation having apparent enhanced bioavailability *(Derendorf, 2005 [A])*. Elimination is by hepatic conjugation, biliary excretion, enterohepatic recirculation, with a terminal half-life of 10 hours.

  Clinical effectiveness is based on the 1996 European Stroke Prevention Study (ESPS-2) *(de Schryver, 2006 [D]; Diener, 1996 [A])* and 2006 ESPRIT *(ESPRIT Study Group, 2006 [A])* studies of secondary prevention of stroke, using dipyridamole in combination with low-dose ASA, marketed in the U.S. as Aggrenox®. Earlier clinical trials of dipyridamole with and without ASA failed to demonstrate benefits, and in retrospect were underpowered.

  Cardiac endpoints in these large stroke trials have shown no selective benefits.

Parenteral Agents

- **Platelet glycoprotein IIb/IIIa antagonists**

  Activation of the platelet surface receptor – P2Y12/Integrin – is the final common pathway for many metabolic activators of platelet aggregation. Agents blocking this activation include naturally occurring polypeptides (snake venoms), synthetic polypeptides and monoclonal antibodies. In addition, these agents also inhibit thrombin generation, which is likely of importance. There are interactions with ASA, clopidogrel, heparins and thrombolytics.

Antiplatelet Agents – Oral

47. Contraindications

- Major hemorrhage
- Hypersensitivity to NSAIDs (aspirin)
- Platelet count less than 50,000
- Syndrome of asthma, rhinitis and nasal polyps

48. Precautions

- Patients at risk of increased bleeding from trauma, surgery or other pathological condition (particularly gastrointestinal and intraocular)
- Alcohol use (three or more drinks/day)
- Pregnancy (third trimester)
- Gastrointestinal symptoms, peptic ulcer disease
- Renal failure
- Severe hepatic insufficiency
- Concomitant use of more than one antithrombotic drug

49. Adverse Effects

Combination of aspirin and clopidogrel and/or combination with warfarin or other anticoagulant have been shown to increase the risk of major bleeding.

Aspirin

Hemorrhage, with underlying hemostatic defects: uremia, hemophilia, anticoagulation therapy. Hemorrhage, without defects: OR 1.6 in high-risk patients *(Antithrombotic Trialists, 2002 [M])*.

Gastric irritation: dose-related *(Chan, 2005 [A]; Dutch TIA Trial, 1991 [A])*

- No better with coated or buffered tablets *(Kelly, 1996 [D])*.
- Influence of concomitant COX-2 inhibitors/NSAIDs
- Withhold NSAIDs for 30 minutes after taking aspirin

Clopidogrel

Thrombotic thrombocytopenic purpura (TTP), sometimes life-threatening, may occur, usually within two weeks of treatment initiation *(Bennett, 2000 [D])*.

Hemorrhage 9%; severe in 1%-2%/year of chronic treatment

Thrombocytopenia

Allergic rash

Diarrhea

Dipyridamole

Systemic vasodilation, with secondary dizziness, syncope, myocardial ischemia

Headache

Hemorrhage is NOT a common problem

50. Pregnancy

Third-trimester risks of placental separation and hemorrhage *(Caritis, 1998 [A]*).

51. Breast-Feeding

Clinical experience limited; risks cannot be entirely ruled out.

52. Monitoring

In most clinical situations, monitoring of oral antiplatelet agents is not required. There are no laboratory methods that have been shown effective in monitoring antiplatelet activity in patients. In patients where the risk of bleeding or thrombotic thrombocytopenic purpura is a concern, monitoring may include:

- CBC/Platelet count
- Fecal blood testing

53. Dosing

Aspirin

For all clinically important endpoint events, oral doses ranging between 81-325 mg/day are sufficient. Higher doses thought in the past to be required for clinical effects have been shown to be unnecessary, and are undesirable because of dose-related gastric and hemorrhagic side effects.

Aspirin Resistance

Some patients at risk, as well as volunteer subjects, have shown variably submaximal responses to aspirin, as assessed by bleeding time and *in vitro* laboratory evaluations of platelet response to ADP (adenosine diphosphate) and other activating agents. Methodologic and statistical issues of sampling, and the functional limitations of available laboratory tests, are likely explanation for the failure to observe such variable dosing requirements in clinical trials.

The ultimate evidence of aspirin resistance would be occurrence of thrombosis and treatment failure, although the presumption of resistance is confounded by the many other factors promoting thrombogenesis at local tissue sites.

Clopidogrel

Loading dose with 300-600 mg *(Savcic, 1999 [A]; Von Beckerath, 2005 [A])* results in more rapid effectiveness, but no scientifically established ideal loading schedule is available. A patient-selective phenomenon of "resistance" has been observed, as with ASA, but again no reliable laboratory test of antiplatelet effect can be recommended.

Clinical studies of combined use of clopidogrel and aspirin have shown mixed results. In patients in the CURE Study with acute coronary syndromes, addition of ASA 75-325 mg to clopidogrel 75 mg resulted in reduced occurrence of the compound endpoints MI, stroke and vascular death, but with severe hemorrhagic events increased by combination therapy, and related to dose of ASA. The increased bleeding was

considered to be acceptable given the benefits attained. In this clinical setting the ASA dose should be 81 mg *(Peters, 2003 [A])*.

Two studies of combined use in secondary stroke prevention concluded that there was no benefit for the same compound endpoints, and the combination consequently discouraged due to increased hemorrhagic risk. The MATCH study found 3% major hemorrhage with combined clopidogrel 75 mg and ASA 75 mg, nearly identical to that in CURE *(Diener, 2004 [A])*. The CHARISMA study of clopidogrel 75 mg and ASA 75-162 mg had only 1.7% combined therapy bleeding (ns versus ASA alone), but still unacceptable in the absence of benefit *(Bhatt, 2006 [A])*.

Dipyridamole

Antiplatelet oral dosing as Aggrenox®, containing 200 mg modified-release dipyridamole plus 25 mg aspirin. Standard-release oral dipyridamole is considered to be unreliable due to erratic absorption *(Derendorf, 2005 [A])*.

54. Treatment of Bleeding Caused by Oral Antiplatelet Agents

Platelet infusion.

55. Key Patient Education Components

Importance of understanding antiplatelet agents and target ranges.

Know and watch for signs of bleeding.

Restrictions for other conditions including deep vein thrombosis, stroke or coronary artery disease. Please refer to related ICSI guidelines for more information.

Importance to adhering to prescribed regimen.

Antiplatelet Agents – Parenteral

56. Contraindications

- Bleeding diathesis or oral anticoagulant use within seven days
- CVA within two years
- History of vasculitis
- Intracranial tumor, arteriovenous malformation or aneurysm
- Major surgery or trauma
- Severe uncontrolled hypertension
- Thrombocytopenia
- Active or recent internal bleeding

57. Precautions

- Concomitant administration with thrombolytics, oral anticoagulants, NSAIDs, dipyridamole and other antiplatelet drugs increase the risk of bleeding.
- A low-dose, weight-adjusted heparin regimen is recommended to minimize the risk of bleeding.

- Minimize arterial and venous punctures, IM injections and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs.
- Arterial sheath should not be removed unless aPTT is 50 seconds or less, OR the activated clotting time is 175 seconds or less, and heparin has been discontinued for at least two hours.
- Full-dose heparin should be stopped at least two hours before femoral artery sheath removal and adequate hemostasis achieved.
- Patients should be maintained on adequate bed rest following sheath removal or discontinuation of IIB/IIIA.
- Thrombocytopenia has been observed; platelet counts should be monitored.

58. Adverse Effects

Major bleeding

Thrombocytopenia (less than 100,000/microliter) less than 1%-2%, usually asymptomatic *(Labinaz, 2007 [M])*.

59. Pregnancy

Little information is known and not all platelet glycoprotein antagonist drugs have been studied. All studies to date have been animal studies.

60. Breast-Feeding

Little information is known but it does not appear that parenteral antiplatelet drugs are excreted in breast milk.

61. Monitoring

In most clinical situations, monitoring of oral antiplatelet agents is not required. There are no laboratory methods that have been shown effective in monitoring antiplatelet activity in patients. In patients where the risk of bleeding is a concern, monitoring may include:

- CBC/platelet count
- fecal blood testing

62. Dosing

Abciximab

IV bolus 0.25 mg/kg plus 0.125 microgm/kg/min infusion; effective in 80% or more in PCI subjects

Half-life at 30 minutes; 65% attachment to platelet surface

Peak effects at 2 hours: receptor blockade, aggregation, bleeding time

Recovery over 12-48 hours

Tirofiban

IV bolus 0.4 microgm/kg/min x 30 min, then 0.1 microgm/kg/min

Renal clearance issues (less than 30 mL/min)

Eptifibatide

IV bolus 180 microgm/kg, infusion 2 microgm/kg/min

Return to normal variable, usually within one hour of discontinuation of infusion

63. Treatment of Bleeding Caused by Parenteral Antiplatelet Agents

Platelet infusion.

64. Key Patient Education Components

Importance of understanding antiplatelet agents and target ranges.

Know and watch for signs of bleeding.

Restrictions for other conditions including DVT, stroke or CAD. Please refer to related ICSI guidelines for more information.

Importance to adhering to prescribed regimen.

65. Mechanical Heart Valves in Patients Who Are Pregnant

Patients with mechanical heart valves who are pregnant or attempting to become pregnant are at high risk and should be managed by an anticoagulation expert. A study has shown that two patients who were pregnant and had 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 valves patients who are pregnant.

Perioperative Management

66. Anticoagulation Bridging

PERIOPERATIVE ANTICOAGULATION		**Procedure Bleeding Risk**	
		LOW	**HIGH**
Patient Thromboembolic Risk	LOW • Atrial fibrillation • VTE history > 3 months since event • Aortic valve	Continue warfarin	Hold warfarin 4 days prior to the procedure (see Table #6)
	HIGH • Recent VTE • Mitral valve • History of CVA	Continue warfarin	Bridging

Risk of Thrombotic Complications in the Absence of Anticoagulation Therapy

Condition	%Thrombotic Risk*
Atrial fibrillation (low risk)	1
Atrial fibrillation (average risk)	5
Atrial fibrillation (high risk)	12
Aortic valve prosthesis (dual-leaflet – St. Jude)	10-12
Aortic valve prosthesis (single-leaflet – Bjork-Shiley)	23
Mitral valve prosthesis (dual-leaflet – St. Jude)	22
Multiple prosthesis (St. Jude)	91

*Annualized

(Ansell, 2008 [R]; Douketis, 2008 [R])

Low Bleeding Risk Procedures

For most dental procedures, a review of the literature has shown that in most cases no change in warfarin is needed *(Ansell, 2008 [R])*. It may be reasonable to allow the patient to "drift" to the low end of their therapeutic INR prior to a dental procedure with a higher risk of bleeding.

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 *(Wahl, 1998 [R]; White, 1995 [D])*.

Other examples of procedures with low bleeding risk include skin biopsies and cataract surgery. Patients who have procedures that are of low bleeding risk can be continued on warfarin anticoagulation without interruption.

For gynecologic and orthopedic surgical patients at low risk for bleeding, the warfarin dose may be lowered four to five days before surgery and the surgery performed at a lower INR (INR 1.3-1.5). The warfarin dose can be increased to the previous dose postoperatively *(Ansell, 2008 [R])*.

Low-Thromboembolic-Risk Patients

Patients with low thromboembolic risk, such as patients with atrial fibrillation without prior CVA or other thromboembolic event, may stop warfarin four doses prior to the procedure and resume wafarin the evening of surgery. Low thromboembolic risk patients undergoing procedures that require perioperative UFH or LMWH for VTE prophylaxis should receive the recommended prophylaxis in addition to resumption of warfarin *(Ansell, 2008 [R]; Heit, 2001 [R]; Kearon, 1997 [R]; Tinmouth, 2001 [D])*.

High Bleeding Risk Procedures for High-Thromboembolic-Risk Patients – Bridging

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. An individual's history of thromboembolism will assist with the decision-making. In general, plan to skip four doses prior to the invasive procedure.

Table 6: Recommended Bridging Schedule

Days Before Procedure	Warfarin	INR	Full-Dose* LMWH** or Therapeutic UFH
5 days prior to procedure	Last dose	Check if not done within two weeks prior.	4-5 days before procedure, start after first missed warfarin dose if at very high risk of thrombosis.
4 days prior to procedure	None	None	4-5 days before procedure, start after first missed warfarin dose if at very high risk of thrombosis.
3 days prior to procedure	None	None	a.m. and p.m. dose
2 days prior to procedure	None	None	a.m. and p.m. dose
1 day prior to procedure	None	Check INR. If INR greater than 1.5, consider 1-2.5 mg Vit K by mouth.	a.m. dose. If UFH is continuous IV infusion, discontinue five hours before surgery. For p.m. dose – if SubQ UFH or LMWH, discontinue dose 12 hours before surgery.
Procedure	Resume at regular dose that evening	None	Start at least 12 hours post procedure – see Annotation #19 of guideline.
1 day after procedure	Regular dose	As indicated – may be skipped	Restart if hemostasis achieved.
2 days after procedure	Regular dose	As indicated	Restart if hemostasis achieved.
3 days after procedure	Regular dose	As indicated	Continue until INR greater than minimum acceptable x 2 day.
4 days after procedure	Regular dose	Daily until INR greater than 2.0 then as indicated.	Discontinue.

* Therapeutic refers to full-dose UFH and LMWH for venous thrombosis and not cardioembolic prevention.

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

Note: Because of long half-life, fondaparinux is not recommended for bridging.

Used with permission from Park Nicollet Health Services.

67. Perioperative Management of Antiplatelet Agents

Patients receiving antiplatelet agents should have these agents stopped 2-10 days prior to a procedure:

- Clopidogrel seven days prior to surgery
- Aspirin 7-10 days prior to surgery
- Ibuprofen two days prior to surgery

Cilostazol (Pletal®) does not appear to prolong bleeding times and has no effect on platelet counts in healthy adults.

68. Neuraxial Blockade Management (Spinal/Epidural)

Table 7a. Management of Antithrombotics Prior to Spinal/Epidural Insertion

Thrombolytics	Low-Molecular-Weight Heparins		Unfractionated Heparin	Warfarin	Antiplatelet Medications	Herbal Therapies
	Once-daily dosing	Twice-daily dosing				
			Platelet count prior to needle insertion for patients receiving heparin for more than 4 days	INR prior to needle insertion for patients on or recently discontinued from chronic warfarin therapy INR for patients who have received one dose of warfarin more than 24 hr prior to needle insertion INR for patients who have received more than one dose of warfarin prior to needle insertion		
Avoid neuraxial block for patients currently receiving thrombolytics Data are not available to clearly outline the length of time needle insertion should be avoided after discontinuation of thrombolytics	Prophylactic dose: needle insertion at least 10-12 hr after the last dose Therapeutic dose: needle insertion at least 24 hr after the last dose	Prophylactic dose: needle insertion at least 10-12 hr after the last dose Therapeutic dose: needle insertion at least 24 hr after the last dose	Consider delaying initiation until after the neuraxial block		NSAIDs – no contraindications Ticlopidine – needle insertion at least 14 days after the last dose Clopidogrel – needle insertion at least 7 days after the last dose Abciximab – needle insertion at least 24-48 hr after the last dose Eptifibatide and tirofiban – needle insertion at least 4-8 hr after the last dose	No contraindi-cations – but may enhance the anticoagulant and/or antiplatelet effects of other medications

Table 7b. Management of Antithrombotics Following Spinal/Epidural Insertion

Thrombolytics	Low-Molecular-Weight Heparins		Unfractionated Heparin	Warfarin	Antiplatelet Medications	Herbal Therapies
	Once-daily dosing	Twice-daily dosing				
Contraindicated for at least 10 days after lumbar puncture, epidural steroid injection, spinal or epidural anesthesia, or puncture of a non-compressible vessel (including most surgical procedures)	Initiate/resume 6-8 hr after needle insertion, second dose no sooner than 24 hr after the first dose	Initiate/ resume 24 hr after needle insertion	Initiate/resume 1 hour after needle insertion		NSAIDs – no contraindications GP IIb/IIIa inhibitors contraindicated for at least 4 weeks after surgery	No contraindications – but may enhance the anticoagulant and/or antiplatelet effects of other medications
	If traumatic insertion, initiate/resume 24 hr after needle insertion	If traumatic insertion, initiate/ resume 24 hr after needle insertion (no mandatory additional delay)	If traumatic insertion, initiate/resume 1 hr after needle insertion (no mandatory additional delay)			
Epidural Catheter Recommendations						
Neuraxial blocks (including epidural catheters) contraindicated for patients currently receiving thrombolytics	Indwelling epidural catheter may be used with once-daily dosing	Indwelling epidural catheter NOT recommended with twice-daily dosing	Indwelling epidural catheter may be used	Indwelling epidural catheter may be used – but should be removed when the INR is less than 1.5 (see below)	NSAIDs – no contraindications GP IIb/IIIa inhibitors – neuraxial blocks (including epidural catheters) contraindicated for patients currently receiving GP IIb/IIIa inhibitors	No contraindications – but may enhance the anticoagulant and/or antiplatelet effects of other medications
			Platelet count prior to indwelling catheter removal for patients receiving heparin for greater than 4 days	INR daily INR < 1.5 prior to indwelling catheter removal		
	Indwelling catheter removal at least 10 hr after the last dose		Indwelling catheter removal at least 2-4 hr after the last dose			
Thrombolytics contraindicated for at least 10 days after catheter removal	Resume at least 2 hr after catheter removal	Initiate at least 2 hr after catheter removal	Resume at least 1 hr after catheter removal		GP IIb/IIIa inhibitors contraindicated for at least 4 weeks after catheter removal	

American Society of Regional Anesthesia and Pain Medicine: Second Consensus Conference on Neuraxial Anesthesia and Anticoagulation April 25-28, 2002, www.asra.com.

New challenges in the management of the anticoagulated patient undergoing neuraxial blockade have arisen as medical standards for the prevention of perioperative venous thromboembolism were established. Likewise, as more efficacious anticoagulants and antiplatelet agents have been introduced, patient management has become more complex.

Regional anesthesia should be avoided in patients with a history of abnormal bleeding.

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 *(Tryba, 1997 [D])*.

General guidelines:

- All patients who receive neuraxial blockade should be monitored closely for developing back pain or signs and symptoms of spinal cord compression (weakness, saddle numbness, incontinence) after injections, during infusions and after discontinuation of infusions.
- Both insertion and removal of neuraxial catheters are significant events. The timing of those events and the timing of any antithrombotic drugs should be taken into consideration, as well as the pharmacokinetics and pharcodynamics of the specific drugs used.
- The emergence of new drugs and unexplained clinical scenarios can render any guideline obsolete. Consultation with an anesthesiologist experienced in regional anesthesia is essential for novel situations.
- The American Society of Regional Anesthesia and Pain Medicine (ASRA) has developed extensive, peer-reviewed guidelines for the practice of regional anesthesia in the presence of antithrombotic therapy and can be used for detailed management. These guidelines are available at http:/www.asra.com.

(Horlocker, 2003 [R])

Spinal hematomas after neuroaxial blockade are very rare (3 in 850,000 in one study) and therefore are difficult to attribute cause and effect. Vandermuelen (1999, [R]) 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 (1998, [NA]) 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 *(Burnett, 1998 [R]; Geerts, 2004 [R]; Horlocker, 1997 [R]; Lumpkin, 1998 [NA])*.

Warfarin with neuraxial blockade

There is no increased risk of perispinal hematoma in patients receiving warfarin postoperatively. However, the mean time to catheter removal was approximately 36 hours, and the majority of patients did not have an INR above 1.5 at the time of removal *(Horlocker, 1994 [D])*.

The ASRA (American Society of Regional Anesthesia) guideline (http://www.asra.com) indicates removal of catheter when INR is less than 1.5 with INR checks perioperatively and daily if the first dose of coumadin was given greater than 24 hours preoperatively *(Horlocker, 1995 [B])*.

Heparin with neuraxial blockade

In general, the most critical time for risk of perispinal hematoma is with indwelling catheter insertion and removal *(Geerts, 2004 [R]; Horlocker, 2001 ; Thompson, 1999 [R]; Wu, 2001 [R])*.

Unfractionated heparin

Unfractionated heparin (UFH) for VTE prophylaxis in patients receiving neuraxial blockade does not appear to have significant risk. The ASRA guideline indicates no change in approach to patients receiving UFH. If the patient has received four or more days of UFH preoperatively, he/she should be assessed for heparin-induced thrombocytopenia (HIT) *(Horlocker, 1995 [B])*. Optimally, the insertion of an epidural catheter occurs after three to four half-lives of the drug has elapsed. Depending on the drug and the renal clearance of the patient, this can be 12-24 hours for UFH or LMWH. An epidural catheter should be removed when the anticoagulation effect is at its minimum, approximately two hours before the next scheduled injection. Anticoagulation therapy may be resumed two hours after the catheter has been removed *(Geerts, 2004 [R])*.

Low-molecular-weight heparin

Low-molecular-weight heparin (LMWH) for VTE prophylaxis in patients receiving neuraxial blockade has some potential issues. In 1997, the U.S. FDA issued a physician advisory for LMWH and risk of spinal hematoma. The agency described 43 U.S. patients who developed perispinal hematoma after receiving the LMWH enoxaparin for VTE prophylaxis. Many of these patients developed permanent neurologic sequelae despite 65% receiving aggressive therapy and laminectomy. The median age of the patients was 78 years, and 78% of the patients were women. The potential risk factors were many, including presence of underlying hemostatic disorder, traumatic needle or catheter insertion, repeated needle insertion attempts or a bloody return in the catheter, catheter insertion or removal in the setting of significant anticoagulation, concurrent use of other antithrombotic agents, use of continuous epidural catheters, anticoagulant dosages and vertebral column abnormalities. There were not large enough patient numbers to develop prevalence data nor establish relative risk for any of the individual risk factors. Therefore, no specific conclusions could be made *(Horlocker, 1997 [R]; Lumpkin, 1998 [NA]; Vandermeulen, 1994 [R]; Wysowski, 1998 [NA])*.

Newer anticoagulant drugs

The use of the newer factor Xa inhibitor, fondaparinux, or the thrombin inhibitors related to hirundin, is a relative contraindication to all regional anesthesia. The emergence of other newer anticoagulant drugs requires that each be evaluated with regard to its safety in combination with regional anesthesia. In all such circumstances, consultation with an anesthesiologist experienced in regional anesthesia is recommended.

Antiplatelet agents with neuraxial blockade

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel) and platelet GP IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) exert diverse effects on platelet function. The pharmacologic differences make it impossible to extrapolate between the groups of drugs regarding the practice of neuraxial blockade.

There is no wholly accepted test that will guide antiplatelet therapy. Careful preoperative assessment of the patient to identify alterations of health that might contribute to bleeding is crucial. These conditions include a history of easy bruisability/excessive bleeding, female gender and increased age.

- NSAIDs appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that will interfere with the performance of neuraxial blocks.
- At this time, there do not seem to be specific concerns as to the timing of single-shot or catheter techniques in relationship to the dosing of NSAIDs, postoperative monitoring or the timing of neuraxial catheter removal.
- The actual risk of spinal hematoma with clopidogrel and the glycoprotein IIb/IIIa antagonists is unknown. Based on labeling and surgical reviews, the suggested time interval between discontinuation of therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel.

- Platelet glycoprotein IIb/IIIa inhibitors exert a profound effect on platelet aggregation. Following administration, the time to normal platelet aggregation is 24-48 hours for abciximab and 4-8 hours for eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function has recovered. GP IIb/IIIa antagonists are contraindicated within four weeks of surgery. Should one be administered in the postoperative period (following a neuraxial technique), the patient should be carefully monitored neurologically.

The concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, unfractionated heparin and LMWH, may increase the risk of bleeding complications. Cyclooxygenase-2 inhibitors have minimal effect on platelet function and should be considered in patients who require anti-inflammatory therapy in the presence of anticoagulation.

69. Key Patient Education Components

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.

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

Age	over 65 years of age
Cardiac	recent MI, atrial fibrillation, hypertension
Endocrine	diabetes
gastrointestinal	history of gastrointestinal hemorrhage, active peptic ulcer disease, hepatic insufficiency
Hematologic/ Oncologic	anemia (hematocrit less than 30), thrombocytopenia (plt less than 50,000 mm_3), platelet dysfunction, coagulation defect, underlying malignancy
Neurologic	history of stroke, dementia, cognitive or psychological impairment
Renal	renal insufficiency, current uremia
Trauma	recent trauma, history of falls (more than three per year within previous year or recurrent, injurious falls)
Alcohol	excessive alcohol intake
Medications/ Natural remedies	use of other medications, such as NSAIDs, or "natural remedies" that intefere with hemostasis; increasing number of medications or "natural remedies"

Anticoagulation Treatment-Related Risk Factors

Duration	increased risk during initial three months of treatment, cumulative risk over time
Intensity	INR greater than 4.0
Variability of control	adequacy of education, support, monitoring and follow-up

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

Risk Factors

- Age 65 or older
- History of stroke
- History of GI bleeding
- Recent MI, HCT less than 30%, creatinine over 1.5 mg/dL, or diabetes mellitus

Sum of Risk Factors	**0**	**1-2**	**3-4**
Risk classification	Low	Intermediate	High
Risk of major bleeding			
Within 3 months	2%	5%	23%
Within 12 months	3%	12%	48%

Reprinted from Beyth RJ, Quinn L, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with wafarin. *Am J of Med* 1998;105:91-99 with permission from Elsevier.

Appendix B – Drug Interactions with Warfarin

Providers should ask patients about any possible changes to their diet, including vitamin and herbal supplements they may be taking. There is limited evidence on the exact effect herbal and other supplements have on warfarin. However, as with other medications, herbal and other supplements have the potential to either alter the clearance of warfarin through various pathways, inhibit the synthesis of vitamin K-dependent coagulation factors, increase the dietary intake of vitamin K and reduce the effectiveness of warfarin, or increase the risk of bleeding through inhibition of platelet function. For more information, see the Reference Bibliography for the NIH conference in the Resources Available section of this guideline.

The international normalized ratio (INR) should be measured more frequently than the usual four-week interval when virtually any drug or herbal medicine is added or withdrawn from the patient treated with warfarin.

(Ansell, 2008 [R])

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 selected drug, food and dietary supplement interactions with warfarin. This table is useful in predicting potential interactions along with the level of supporting evidence and direction of the interaction.

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

Drug, Food, and Dietary Supplement Interactions With Warfarin by Level of Supporting Evidence and Direction of Interaction (Section 1.1.2)*

Level of Causation	Antiinfectives	Cardiovascular	Analgesics, Antiinflammatories, and Immunologics	CNS Drugs	GI Drugs and Food	Herbal Supplements	Other Drugs
Potentiation							
Highly probable	Ciprofloxacin Cotrimoxazole Erythromycin Fluconazole Isoniazid Metronidazole Miconazole Oral Gel Miconazole Vag Supp Voriconazole	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfinpyrazone (biphasic with later inhibition)	Phenylbutazone Piroxicam	Alcohol (if concomitant liver disease) Citalopram Entacapone Sertraline	Cimetidine Fish oil Mango Omeprazole	Boldo-fumugreek Quilinggao	Anabolic steroids Zileuton
Probable	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Acetaminophen Aspirin Celecoxib Dextropropoxphene Interferon Tramadol	Disulfiram Chloral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)	Grapefruit	Danshen Don quai Lycium Barbarum 1 PC-SPES	Fluorouracil Gemcitabine Levamisole/fluorouracil Paclitaxel Tamoxifen Tolterodine
Possible	Amoxicillin Amoxicillin/tranexamic rinse Chloramphenicol Ciprofloxacin Miconazole Topical Gel Nalidixic Acid Norfloxacin Ofloxacin Saquinavir Terbinafine	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone	Celecoxib Indomethacin Leflunomide Propoxphene Rofecoxib Sulindac Tolmetin Topical salicylates	Felbamate	Orlistat	Danshen/methyl salicylates	Acarbose Cyclophosphamide/ methotrexate/ fluorouracil Curbicin Danazol ifosphamide Trastuzumab
Highly improbable	Cefamandol Cefazolin Sulfisoxazole	Bezafibrate Heparin	Levamisole Methylprednisolone Nabumetone	Fluoxetine/diazepam Quetiapine			Etoposide/carboplatin Levonorgestrel
Inhibition							
Highly probable	Criseofulvin Nafcillin Fibavirin Rifampin	Chlestyramine	Mesalamine	Barbiturates Carbamazepine	High vitamin k content foods/enteral feeds Avocado (large amounts)		Mercaptopurine
Probable	Dicloxacillin Ritonavir	Bosentan	Azathioprine	Chloradiazeposide	Soy milk Sucralfate	Cimseng	Chelation therapy Influenza vaccine Multivitamin supplement Raloxifene HCL
Possible	Terbinafine	Telmisartan	Sulfasalazine		Sushi containing seaweed		Cyclosporine Etretinate Ubidicarenone
Highly improbable	Cloxacillin Nafcillin/dicloxacillin Teicoplanin	Furosemide		Propofol		Green tea	

*Data from Holbrook et al[54] with permission.

Used with permission Chest 2008; 133;160-198 DOI 10.1378/chest.08-0670, Pharmacology and Management of the Vitamin K Antagonists: ACCP Evidence-Based Clinical Practice Guidelines (8th edition). This information is current as of January 22, 2009. For the most up-to-date medication and prescribing information, consult with your pharmacy or consider the following sources: www.epocrates.com, www,micromedex.com, www.uptodate.com, www.pdr.net.

Appendix C – 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
- CYP2CP and/or VKORC1 genotype

The information in this table was compiled from manufacturer package inserts, www.epocrates.com, www.micromedex.com, www.uptodate.com, www.pdr.net and is current as of January 22, 2009. For the most up-to-date medication and prescribing information, consult with your pharmacy or consider the following sources: www.epocrates.com, www.micromedex.com, www.uptodate.com, www.pdr.net.

Appendix D – 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 THAT MAY AFFECT INR:

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 anticlotting 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 breast-feeding, 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
4. Hair loss

Used with permission from Mayo Clinic.

Appendix E – Example of a Heparin Nomogram

Several protocols for managing heparin therapy have been shown to more rapidly achieve therapeutic anti-coagulation (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:

aPTT level*	Dosage adjustment
less than 35 seconds	80 units/kg bolus, then increase infusion rate by 4 units/kg/hour
35-45 seconds	40 units/kg bolus, then increase infusion rate by 2 units/kg/hour
46-75 seconds	no change
71-90 seconds	decrease infusion rate by 2 units/kg/hour
greater than 90 seconds	hold infusion 1 hour, then decrease infusion rate by 3 units/kg/hour

The aPTT levels are drawn six hours after any dosage change, adjusting heparin infusion by the sliding scale until aPTT is therapeutic (46 to 70 seconds). When two consecutive aPTTs are therapeutic, order aPTT (and readjust 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.

Used with permission from Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a 'standard care' nomogram: a randomized controlled trial. *Ann Intern Med* 1993;119:874-81.

Appendix F – Glossary of Abbreviations

aPTT	Activated partial thromboplastin time
CNS	Central nervous system
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
FFP	Fresh frozen plasma
GI	Gastrointestinal
HCT	Hematocrit
HAT	Heparin-associated thrombosis
HIT	Heparin-induced thrombocytopenia
IM	Intramuscular
INR	International normalized ratio
	$INR = (\text{patient PT/mean normal PT})^{ISI}$
ISI	International sensitivity index
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
PCC	Prothrombin complex concentrate
PE	Pulmonary embolism
PT	Prothrombin time
UFH	Unfractionated heparin
VTE	Venous thromboembolism

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Brief Description of 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 Foreword of the guideline.

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This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Knowledge Resources
- Resources Available

Knowledge Resources

Criteria for Selecting Resources

The following resources were selected by the Antithrombotic Therapy Supplement guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

Resources Available to ICSI Members Only

ICSI has a wide variety of knowledge resources that are ***only*** available to ICSI members (these are indicated with an asterisk in far left-hand column of the Resources Available table). In addition to the resources listed in the table, ICSI members have access to a broad range of materials including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Resources, go to http://www.icsi.org/improvement_resources. To access these materials on the Web site, you must be logged in as an ICSI member.

The resources in the table on the next page that are not reserved for ICSI members are available to the public free-of-charge.

Resources Available

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	AMA Foundation	Site contains downloadable print education materials on cardiovascular and other topics in a wide range of languages.	Health Care Professionals; Patients and Families	http://www.healthinfotranslations.com
	American College of Chest Physicians	ACCP Consensus Conference guidelines supporting anticoagulation clinics.	Providers	American College of Chest Physicians. Seventh ACCP Consensus Conference on Antithrombotic Therapy. Chest September 2004 Supplement. 1-800-343-2227
	Ansell, Jack	"How-to" manual for establishing anticoagulation clinics	Providers	Managing Oral Anticoagulation Therapy: Clinical and Operational Guidelines
	Anticoagulation Forum	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.	Providers	http://www.acforum.org
	CareInternet	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.	Providers and patients	http://www.careinternet.com
	Heart Rhythm Society	**Heart Rhythm Society:** Comprehensive site includes research updates, guidelines and a reference center for professionals. Patient and public links include a heart information center, electrophysiology referral information and patient stories. Education materials available. Spanish and English.	Health Care Professionals; Patients and Families	http://www.hrsonline.org
	Journal of the American Medical Association – Patient Page	**JAMA Patient Page:** A public service of the Journal of the American Medical Association. The key objective of JAMA is to promote the science and art of medicine and the betterment of the public health.	Health Care Professionals; Patients and Families	http://www.jama.ama-assn.org/cgi/collection/patient_page

* Available to ICSI members only.

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	KRAMES Communications® 1998	Single sheet describing importance of diet, helpful hints and when to call the doctor.	If You Take Coumadin®	#5520/9807 https://shop.krames.com/
	National Alliance for Thrombosis and Thrombophilia (NATT)	A patient-led advocacy organization that includes many of the nation's foremost experts on blood clots and blood clotting disorders.	Patients and Families	http://stoptheclot.org/
	National Board of Anticoagulation Providers	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.	Providers	http://www.acforum.org National Board of Anticoagulation Providers c/o Anticoagulation Forum Boston University Medical Center Room E-113 88 E. Newton St. Boston, MA 02118-2395
	National Institute of Health (NIH)	Reference Bibliography for the NIH Conference on Dietary Supplements, Coagulation, and Antithrombotic Therapies – a compilation of studies on the effects of vitamins, minerals, fatty acids, herbal/other botanical supplements, other dietary supplements and foods on antithrombotic drugs.	Providers and Patients	http://www.nhlbi.nih.gov/meetings/coagulation
	Park Nicollet Health Services	Deep Vein Thrombosis (DVT) – a patient education pamphlet for DVT.	Patients	http://www.icsi.org
	Vascular Disease Foundation	A non-profit educational organization dedicated to increasing awareness of prevention, diagnosis and management of vascular diseases. This Web site is dedicated to reducing death and disability from vascular diseases and improving vascular health.	Health Care Professionals	http://www.vdf.org

* Available to ICSI members only.