



INSTITUTE FOR CLINICAL
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Health Care Guideline: Antithrombotic Therapy Supplement

**Tenth Edition
April 2011**

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- health care teaching institutions;
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Disclosure of Potential Conflict of Interest

In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. It is not assumed that these financial interests will have an adverse impact on content. They are simply noted here to fully inform users of the guideline.

Dr. Bruce Burnett disclosed grant support from Boehringer Ingelheim for his investigatory role with dabigatran.

Dr. Stephen Kopecky disclosed pending grant support from Hormel Specialty Foods. Dr. Kopecky is a consultant for Applied Clinical Intelligence and for Prime Therapeutics. He consults without payment for Biophysical and Pinnacle Care. Dr. Kopecky serves on the Board of Stratis Health.

Dr. Timothy Miley received travel and conference support from the American Society of Clinical Pathology for matters concerning the Board of Certification, Board of Governors. He also received travel support from the American Society of Hematology for work on the Practice Committee, on which he is a member.

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

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Evidence Grading

A consistent and defined process is used for literature search and review for the development and revision of ICSI guidelines. Literature search terms for the current revision of this document include anticoagulation for age 75+; reversal agents to fondaparinux; warfarin genetic testing; perioperative bridging; platelet aggregation inhibitors and thrombosis; platelet glycoprotein GPIIb-IIIa inhibitors and thrombocytopenia inhibitors and thrombosis; dabagatran, a direct thrombin inhibitor; ticagrelor; factor Xa inhibitor; pregnancy and antithrombotic; poor CYP2C19 metabolizer and clopidogrel from May 2009 – November 2010.

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

Evidence citations are listed in the document utilizing this format: (*Author, YYYY [report class]; Author, YYYY [report class] – in chronological order, most recent date first*). A full explanation of ICSI's Evidence Grading System can be found on the ICSI Web site at <http://www.icsi.org>.

Class	Description
Primary Reports of New Data Collections	
A	Randomized, controlled trial
B	Cohort-study
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
D	Cross-sectional study Case series Case report
Reports that Synthesize or Reflect upon Collections of Primary Reports	
M	Meta-analysis Systematic review Decision analysis Cost-effectiveness analysis
R	Consensus statement Consensus report Narrative review
X	Medical opinion

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Foreword

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: [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](#), on the Web site: <http://www.icsi.org>; (cardiovascular link: http://www.icsi.org/guidelines_and_more/gl_os_prot/cardiovascular/).

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 suprathreshold 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 can be found on the [Definitions](#) page.

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Scope and Target Population

This guideline supplement is targeted for any adult patient receiving antithrombotic therapy. Please refer to [related ICSI guidelines](#) for specific target populations.

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Clinical Highlights

- There are no circumstances under which patients absolutely should or should not receive anticoagulation therapy, with the exception of life-threatening bleeding. 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, 44, 45, 47, 54, 55, 57, 64, 65, 67*)
- 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 international normalized ratio) and/or reduce the effectiveness of platelets (not detected by the international normalized ratio). (*Annotation #7*)

Foreword

- 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, 52, 63, 72*)
- 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 his or her treatment regimen. (*Annotations #11, 21, 25, 35, 52, 62, 63, 72*)
- Patients with mechanical heart valves who are pregnant have complex anticoagulation needs and should be managed by an anticoagulation expert. (*Annotations #4, 16*)
- Recent concerns about concomitant use of proton pump inhibitors (PPI) and clopidogrel ought to be addressed on a patient-by-patient basis with discontinuation of PPI if there is no definite indication for its use; H2 blockers could be considered if acid-suppression is desired. (ICSI Antithrombotic work group consensus-based recommendation). (*Annotation #53*)
- Dabigatran has been FDA approved for use only in non-valvular atrial fibrillation as an alternative to warfarin for stroke prevention. (*Annotation #37*)

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Related ICSI Scientific Documents

Guidelines

- [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](#)

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Definitions

aPTT	Activated partial thromboplastin time
AUC	Area under the drug plasma concentration – time curve
CNS	Central nervous system
CV	Cardiovascular
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
	$INR = (\text{patient PT}/\text{mean normal PT})^{ISI}$
ISI	International sensitivity index
LMWH	Low-molecular-weight heparin
MI	Myocardial infarction
NSAID	Non-steroidal anti-inflammatory drug
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PT	Prothrombin time
TIA	Transient ischemic attack
UFH	Unfractionated heparin
VTE	Venous thromboembolism

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Algorithm Annotations

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/mm³) 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 increased risk in bleeding against the potential decreased risk of thromboembolism when evaluating warfarin therapy.

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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 [Annotation #3, "Adverse Effects,"](#) for additional information about predicting the risk of bleeding for individual patients.

Pregnancy

See [Annotation #4, "Pregnancy \(Warfarin\) – High Risk."](#)

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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. 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

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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 (*Levine, 2004 [R]; Sebastian, 2000 [R]; Landefeld, 1993 [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, 2005 [R]; Hart, 1998 [M]; Hart, 1995 [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.**

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

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.

(*Talmadge, 2003 [D]; Sallah, 1997 [R]; Abdelmalek, 1995 [D]; Ansell, 1993 [R]; Hyman, 1987 [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]; Jamal, 1998 [B]; Umlas, 1988 [D]; Kwong, 1978 [D]; Cornbleet, 1957 [D])

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4. Pregnancy (Warfarin) – High Risk

Recommendations regarding the use of warfarin during pregnancy are difficult due to lack of prospective data. Clinical guidelines are based mainly on retrospective data.

The manufacturer of warfarin states that it is contraindicated during pregnancy secondary to embryopathy associated with use during the first trimester, weeks 6-12 and CNS abnormalities from exposure during any trimester. The risk of embryopathy appears to be between 4% and 10%. The risk may be lower if the dose of warfarin is less than 5 mg per day.

If the mother is taking warfarin at the time of delivery, the rate of fetal intracranial hemorrhages during delivery is increased. If patients remain on warfarin during pregnancy, warfarin should be discontinued and continuous intravenous unfractionated heparin should be started 2-3 weeks prior to delivery (Bates, 2004 [R]).

In patients with mechanical heart valves, the decision of whether to continue warfarin or use unfractionated heparin or low-molecular-weight heparin during the first trimester and throughout pregnancy should be made after a discussion with an anticoagulation expert with regards to the risk and benefits (Nishimura, 2008 [R]). For further recommendations, please see the ACC/AHA 2008 Guideline Update on Valvular Heart Disease: Focused Update on Infective Endocarditis.

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5. Breastfeeding

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

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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]).

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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 phospholipid; 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 (*Fairweather, 1998 [R]*; *Adcock, 1997 [B]*).

- 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.

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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]*).

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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 (*Crowther, 1999 [A]*; *Beyth, 1998 [B]*).

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

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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]; Kovacs, 2003 [A]; Hylek, 2001 [B]; Harrison, 1997 [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 end point (*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 Venous Thromboembolism Diagnosis and Treatment](#) 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 #74, "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.

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.

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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 and heparins can affect the INR. Please refer to [Annotations #36-52, "Direct Thrombin Inhibitors,"](#) for more information.

Initiation of Warfarin

The benefits and risks of the addition of aspirin, heparin and/or a low-molecular-weight heparin to warfarin during initiation vary from disease to disease. Please see the disease specific ICSI guidelines on the Web site: <http://www.icsi.org> (cardiovascular link: http://www.icsi.org/guidelines_and_more/gl_os_prot/cardiovascular/).

- [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](#)

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 (*Crowther, 1999 [A]; Beyth, 1998 [B]*).

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.

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]; O'Connell, 2000 [D]; Blann, 1999 [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 end points, 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]; Wilt, 1995 [D]; Cortelazzo, 1993 [D]; Garabedian-Ruffalo, 1985 [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 warfarin was managed

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by anticoagulation clinics (*Beyth, 2000 [B]*; *Chiquette, 1998 [C]*; *Wilt, 1995 [D]*; *Cortelazzo, 1993 [D]*; *Garabedian-Ruffalo, 1985 [D]*). See the Quality Improvement Support section under Resources Table 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]*).

Patient Self-Testing and Self-Management

Although patient self-testing of the INR in warfarin therapy has been practiced successfully in Europe for many years, this approach to care has not been widely adopted in the United States. In 2008, the Centers for Medicare and Medicaid Services (CMS) expanded the covered indications for patient self-testing of the INR to include the common conditions of atrial fibrillation and venous thromboembolism (*CMS, 2008 [NA]*). Despite this change, only 1% of warfarin patients in the United States participate in a self-testing program (*Finkel, 2010 [X]*).

Previous studies have suggested that patient self-testing resulted in superior outcomes related to stroke, major bleeding and death (*Heneghan, 2006 [M]*). However, a recent large randomized clinical trial showed equivalent outcomes when weekly patient self-testing was compared to monthly, high-quality testing in an anticoagulation clinic. The patient self-testing group did show significant improvement of the secondary outcomes of time within the therapeutic range, patient satisfaction with anticoagulation therapy and quality of life (*Matchar, 2010 [A]*).

A consensus guideline has been published detailing a recommended approach to developing a patient self-testing and/or self-management program (*Ansell, 2005 [R]*). Critical elements of a program include appropriate patient (or caregiver) selection for adequate cognition, vision and dexterity, a structured, face-to-face patient education program carried out by a trained staff, formal patient testing to confirm understanding of required information, weekly patient testing and ongoing supervision by a physician or training center. Coagulometers selected for self-testing should give similar results to the laboratory INR testing. These meters should be compared to the laboratory INR or a central point-of-care laboratory instrument at least annually.

At present, patient self-management is not approved by Medicare. Self-management programs would require ongoing support from a physician or anticoagulation clinic for a variety of issues including situations where maintaining appropriate anticoagulation were difficult, planned surgical intervention requiring bridging and ongoing education (*Ansell, 2005 [R]*).

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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)
Chronic atrial fibrillation	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 Thromboembolism Diagnosis and Treatment guideline.
Venous thromboembolism prophylaxis	See ICSI Venous Thromboembolism Prophylaxis guideline.

* For the first three months post valve insertion for a) bioprosthesis in mitral position, and b) patients with a history of systemic embolism; consider long-term warfarin anticoagulation for patients with co-existing risk factors, e.g., atrial thrombus (until thrombus resolution), atrial fibrillation, hypercoagulable state, low ejection fraction.

(Hirsh, 2008 [R])

For specific treatment recommendations, please see the ICSI [Venous Thromboembolism Diagnosis and Treatment](#) guideline or the [Venous Thromboembolism Prophylaxis](#) guideline.

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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. Vitamin K doses greater than 5 mg are associated with an increased likelihood of substantial, prolonged warfarin resistance. In patients with an INR of 5-8.9 and no significant bleeding, the CHEST guideline recommends administration of a vitamin K dose of 1-2.5 mg. Although a 1 mg dose is not currently available, the margin of error when splitting a 5 mg tablet into 4 doses, resulting in 1.25 mg dosages, is not clinically different from a 1 mg dose and may be utilized.

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

Important Considerations for Vitamin K Dosing

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

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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 erratic correction of INR and resistance to warfarin (Ansell, 2008 [R]; Shields, 2001 [B]; Whitling, 1998 [C]).

Table 2: Correction of Supratherapeutic Anticoagulation 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 K₁ 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)

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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

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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.

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

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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.

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Heparin (Unfractionated and Low-Molecular-Weight)

12. Introduction

In October of 2009 the FDA notified health care professionals of a change to heparin that standardized the USP unit dose with the WHO International Standard unit dose. This change resulted in an approximately 10% reduction in anticoagulant activity compared to heparin prepared using the previous USP Monograph potency. The FDA recommends that health care professionals "exercise clinical judgment in determining the dose of heparin for a patient and consider the clinical circumstances where the potency decrease may require dosage adjustments and more frequent monitoring," particularly when heparin is administered as a bolus intravenous dose and an immediate anticoagulant effect is clinically important. Due to the high inter-patient variability in heparin clearance (± 1.18 mL/min/kg) (*Bauer, 2001 [R]*), therapeutic heparin dose is highly individualized per patient and highly reliant on PTT or heparin assay monitoring and dose adjustment. Although a small downward bias may be observed overall, built-in PTT/ACT protocols and bolus dose ranges may negate the need for broad, empiric policy change.

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.

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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]*).

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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

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- Hemorrhagic stroke
- Status post brain, spinal or ophthalmologic surgery
- Uncontrolled arterial hypertension
- Diabetic retinopathy
- Impaired renal function (CrCl < 50 mL)

CrCl via Cockcroft-Gault	Dalteparin	Enoxaparin
CrCl 30-50 mL/min	No accumulation occurs and no dosing adjustment is recommended, per the package insert.	A 15%-20% accumulation occurs with > 14 day use. No dosing adjustment is recommended, per package insert.
CrCl < 30 mL/min	No accumulation has been demonstrated for up to one week. Package insert recommends: use with caution.	A 40%-50% accumulation occurs. Per package insert, reduce prophylactic doses to 30 mg subcutaneous once daily and treatment doses to 1 mg/kg subcutaneous once daily.

(Ansell, 2008 [R])

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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 than 50% decrease in platelet count from baseline labs while on heparin (Warkentin, 2007 [R]).
- HIT should be suspected if the patient experiences a new thrombotic event within 5 to 14 days of initiating heparin therapy, even if the heparin has been discontinued (Warkentin 2008a [R]).
 - In non-cardiac post-surgical patients, HIT should be suspected when the platelet count falls 50% from the post-operative platelet count peak (Warkentin, 2007 [R]).
 - Cardiac surgery patients who develop a 30% decrease in platelet count between postoperative day 5 and 10 should also be suspected of having HIT.
 - Cardiac surgery patients who develop thrombocytopenia that arises within 72 hours of the procedure and persists beyond postoperative day 5 without a second drop between postoperative days 5 and 10 rarely show clinical evidence of HIT (Selleng, 2010 [DJ]).
- All heparin should be stopped in patients suspected of having HIT until antibody test results are available.

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- 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 direct thrombin inhibitor 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 (*Hirsh, 2004 [R]; Levine, 2004 [R]; Campbell, 1996 [A]; Hull, 1990 [A]*).

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. HIT should also be suspected if the patient experiences a new thrombotic event within 5 to 14 days of initiating heparin therapy, even if the heparin has been discontinued (*Warkentin 2008a [R]*).

In the first 72 hours following the procedure, however, post-cardiac surgery patients frequently show a 40% to 50% decrease in the platelet count that persists beyond postoperative day 5. Furthermore, 25%-70% of these patients will develop antiplatelet factor 4 (PF4)-heparin antibodies, the causative agent in HIT. Only a small percentage of these antibody-positive patients with early, persistent and stable thrombocytopenia will develop clinical HIT. Further study correlating the strength of anti-PF4-heparin antibody assays, platelet activation assays and clinical outcomes of this group of patients is required before development of definitive recommendations (*Gruel 2010 [R]; Selleng, 2010 [D]*).

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 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.

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 generics are FDA approved: argatroban, lepirudin, and most recently, bivalirudin (*Warkentin, 2004a [R]; Warkentin, 2004b [R]; Warkentin, 2003 [R]*).

The off-label use of fondaparinux has been suggested as an alternative to DTI therapy in HIT given its long half-life and lack of significant effect on the INR as well as the Protein C pathway (*Warkentin, 2010 [R]*).

Algorithm Annotations

Although fondaparinux therapy can result in development of anti-PF4/heparin antibodies, they usually do not result in platelet activation. Three cases of HIT related to fondaparinux therapy have been reported (*Rota, 2008 [D]*; *Warkentin, 2008 [D]*; *Warkentin, 2007 [D]*). Further study is required prior to recommendation of fondaparinux as a therapy in HIT.

Warfarin therapy alone is contraindicated in the setting of acute HIT (*Warkentin, 2010 [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 lepirudin are too high. Therefore, lower doses are recommended (see [Annotation #50, "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 #36-52, "Direct Thrombin Inhibitors,"](#) for more information.

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16. Pregnancy (Heparin)

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.

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17. Breastfeeding

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

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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]*)

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19. Dosing

Testing should be obtained before initiation of UFH:

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

Algorithm Annotations

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 Thromboembolism Prophylaxis guideline and ICSI Venous Thromboembolism 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 (*Raschke, 1993 [A]*; *Cruickshank, 1991 [B]*). Each institution must develop its own nomograms based upon their unique specific therapeutic ranges.

A standard weight-based protocol for heparin administration should not be used for patients receiving parenteral platelet receptor glycoprotein IIb/IIIa antagonist (abciximab, tirofiban, eptifibatid) and/or thrombolytics (alteplase, reteplase, tenecteplase, streptokinase). 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.

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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.

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

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

(*Hirsh, 2004 [R]*)

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21. Key Patient Education Components

Importance of understanding heparin assays, INRs and target ranges.

Know and watch for signs of bleeding.

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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]*).

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23. Dosing

Key Point:

- Prophylactic doses are lower than therapeutic and carry lower bleeding risks. However, in patients with acute thrombosis and cardioembolic risks, therapeutic dosing is generally recommended.

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.

Algorithm Annotations

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]*).

Prophylactic doses of the low-molecular-weight heparins are less than therapeutic doses and carry lower bleeding risks. However, in patients with acute thrombosis or increased thrombosis risk, therapeutic dosing is generally necessary.

Please see the disease specific ICSI guideline recommendations on the ICSI Web site: <http://www.icsi.org> (cardiovascular link: http://www.icsi.org/guidelines_and_more/gl_os_prot/cardiovascular/):

- [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](#)

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24. Correction of Supratherapeutic Anticoagulation Caused by LMWH

No agent, including fresh frozen plasma (FFP) and vitamin K, is effective for complete reversal of supra-therapeutic 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.

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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 included in the Quality Improvement Support section.

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Synthetic Pentasaccharide (Fondaparinux)

26. Introduction

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

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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 (Cockcroft-Gault) < 30 mL/minute.

Secondary increased risk for major bleeding episodes.

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.

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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.
- Renal impairment (CrCl 30-50 mL/min).

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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.

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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.

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31. Breastfeeding

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

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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, 2010 [R]*). Fondaparinux is not recommended for patients with platelets less than 100,000/mm³ 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](#).

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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/mm³.

Contraindications:

- Dialysis-dependent renal failure
- A creatinine clearance < 30 mL/min.

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 3: 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 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

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

Please refer to the ICSI [Venous Thromboembolism Diagnosis and Treatment](#) and [Venous Thromboembolism Prophylaxis](#) guidelines for more information.

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34. Correction of Supratherapeutic Anticoagulation Caused by Fondaparinux

There is no antidote for excessive bleeding due to fondaparinux. Recombinant 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.

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

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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.

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Direct Thrombin Inhibitors

36. Introduction

Direct thrombin inhibitors (DTIs) – argatroban, bivalirudin, lepirudin, dabigatran – 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. Parenteral direct thrombin inhibitors have been available for nearly a decade and are used most frequently in cardiovascular procedures and for the treatment of patients with heparin induced thrombocytopenia. The oral direct thrombin inhibitor, dabigatran, was recently FDA approved for use in patients with non-valvular atrial fibrillation.

Consultation with a hematologist or anticoagulation expert may be helpful when using these new anticoagulant drugs because of both drug and disease complexities.

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37. Oral Direct Thrombin Inhibitors (Dabigatran)

Key Considerations for Dabigatran

- Has been FDA approved for use only in non-valvular atrial fibrillation as an alternative to warfarin for stroke prevention. (*Wann, 2011 [R]*)

Algorithm Annotations

- Patients most likely to benefit from dabigatran are patients unable to achieve and sustain a stable INR or those unable to use warfarin due to management issues (*Wallentin, 2010 [A]*).
- Like warfarin, it requires the same careful risk/benefit assessment for patients at great risk for hemorrhage (*Stangier, 2009 [R]*).
- Caution should be used in patients with CrCl < 30 mL/min as drug accumulation will occur and there is no clinical experience in this patient population (*Stangier, 2009 [R]*).
- Prior to procedures the drug must be held, the duration of which depends on a patient's renal clearance and bleed risk from procedure (*van Ryn, 2010 [R]*).

Dabigatran is rapidly absorbed with peak dabigatran levels achieved within 2 to 4 hours. The bioavailability of dabigatran following oral administration of dabigatran etexilate is between 3% and 7%. The half-life of dabigatran is 12-17 hours, and steady-state concentrations are reached within 2 to 5 days after multiple doses. Dabigatran is renally eliminated so clearance is significantly influenced by renal function.

Product care information

Dabigatran deteriorates quickly when exposed to humidity and must be kept in its original package to keep dry. Dabigatran is manufactured in bottles of 60 capsules (a 30 day supply) or in blister packs sealing each capsule separately. Bottles from the manufacturer contain a desiccant in the lid to ensure stability for 30 days after opening. Capsules packaged in bottles should be kept tightly closed and should NOT be placed in any other container, such as weekly dosing containers used to enhance adherence, as such containers cannot guarantee moisture resistance. Patients should be instructed to keep the product in its original container and close the cap tightly after each use.

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38. Dosing

The FDA approved dose of dabigatran for use in non-valvular atrial fibrillation is 150 mg twice daily for patients with creatinine clearance (CrCl) > 30 mL/min and 75 mg twice daily in patients with CrCl of 15 - 30 mL/min. The lower renal dose is based on pharmacokinetic data, and there is no clinical experience available. Use in patients with CrCl < 15 mL/min or patients receiving dialysis is not recommended. If a dose is missed, and that dose was to be taken in the next six hours, the patient can wait until the next dose. For example, if the 8:00 a.m. morning dose is missed, and the patient realizes this at 4:00 p.m., then it is recommended that the patient wait until the next dose at 8:00 p.m. However, if the patient realized at 11:00 a.m. that the 8:00 a.m. dose was missed, then the dose can be taken at 11:00 a.m.

Indications

Atrial fibrillation

A large randomized controlled open label trial (Randomized Evaluation of Long-Term Anticoagulation Therapy, RE-LY) compared dabigatran 150 mg twice daily to adjusted dose warfarin to achieve a target INR range of 2.0-3.0 in patients with atrial fibrillation and at least one additional risk factor for stroke. The primary objective of the study was to determine if dabigatran was non-inferior to warfarin at reducing stroke (ischemic or hemorrhagic) and systemic embolism. Dabigatran 150 mg twice daily was associated with a lower incidence of stroke (1.11%/year) compared to warfarin (1.69%/year) with similar hemorrhagic rates. Major bleeding occurred at a rate of 3.11% per year for dabigatran and 3.36% per year for warfarin.

A subgroup analysis of the RE-LY study demonstrated that the majority of the benefit of dabigatran was seen when compared to warfarin patients who were poorly controlled. These poorly controlled warfarin patients had the greatest proportion of bleeding and thrombotic complications.

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39. Contraindications and Precautions

Patients with prohibitive bleed risks were not included in studies of dabigatran. As with all anticoagulants, extreme caution should be used in giving dabigatran to patients with bleeding diatheses, falls risk, alcohol abuse or compliance issues. An individual patient's risk of thrombosis versus risk of bleeding needs to be assessed before use of this or any anticoagulant.

Pregnant patients and those with valvular heart disease have not been studied and are not yet candidates for this drug.

Dose adjustment or avoidance of drug should be considered in patients with severe renal insufficiency, especially if the patient's kidney function is in flux.

Side Effects

Bleeding

Although overall bleed risk was similar to warfarin, there was a significantly higher incidence of gastrointestinal bleeding while a significantly lower incidence of intracranial hemorrhage in the patients taking dabigatran. Also demonstrated in a subgroup analysis was a trend toward a higher incidence of major bleeding in patients 75 years of age and older on dabigatran.

Dyspepsia

A significant (5.5%) number of patients in the trial experienced a severe form of dyspepsia on dabigatran. Elevation of ALT or AST greater than three times the upper limit of normal was similar for both doses of dabigatran and warfarin.

Myocardial infarction

The RE-LY trial also demonstrated a statistically significant increase in the rate of myocardial infarction in patients treated with dabigatran (0.7% per year) as compared to a rate of 0.5% per year in patients treated with warfarin. This translated into a relative risk of 1.38 (95% confidence interval, 1.00-1.91; P=0.048). Further analysis (*Lip, 2010 [A]*) was undertaken by reviewing pooled data from multiple trials, the largest being RE-LY, to look at this effect. The analysis revealed that among patients with atrial fibrillation, warfarin may result in a lower risk of myocardial infarction. The data suggests there may be an intrinsic myocardial protective effect from warfarin as opposed to non-warfarin anticoagulants.

Drug Interactions

Similar to other anticoagulants, aspirin and other anti-platelet agents have been associated with a significant increase in risk for hemorrhagic complications. Unless strongly indicated anti-platelet agents should be avoided in patients taking dabigatran.

Dabigatran etexilate, the prodrug of dabigatran, is a p-glycoprotein substrate, and the active drug dabigatran is not. The absorption of the prodrug dabigatran etexilate can be altered by p-glycoprotein inhibitors and inducers. Drugs that inhibit p-glycoprotein (e.g., amiodarone, clarithromycin, diltiazem, verapamil) can increase the area under the drug plasma concentration curve (AUC) of dabigatran. Administering dabigatran more than two hours before a p-glycoprotein inhibitor may minimize the effect of the inhibitor on dabigatran absorption. Drugs that induce p-glycoprotein (e.g., rifampin) decrease the AUC of dabigatran. Separating the dose of dabigatran and a p-glycoprotein inducer is not thought to minimize the magnitude of the interaction. Therefore, the concomitant use of dabigatran and p-glycoprotein inducers should be avoided if possible (*Horn, 2010 [X]*).

Administration of dabigatran etexilate capsules with pantoprazole resulted in a reduction of dabigatran's AUC by 20%-30% and its peak concentration by 45% (*Horn, 2010 [X]*; *Stangier, 2008 [A]*, *Trocóniz, 2007 [B]*; *Stangier, 2005 [B]*). In the RE-LY trial, concomitant use of proton pump inhibitors, H2 receptor antagonists did not appreciably change the trough concentration of dabigatran (*Connolly, 2009 [A]*).

40. Monitoring and Effect on Laboratory Tests

Routine monitoring of dabigatran is not required. Specialized laboratory assays (ecarin clotting time, ECT; dilute thrombin time, dTT) are required for accurate assessment of plasma dabigatran levels; however these assays are not widely available. Dabigatran prolongs the clotting times of routine, more widely available assays (thrombin clotting time, TT; activated clotting time, ACT; prothrombin time, PT; activated partial thromboplastin time, aPTT). However, these assays do NOT reliably predict plasma dabigatran levels and do not provide an accurate assessment of risk of surgical hemorrhage in patients on dabigatran. The information provided by these assays is limited to whether there is residual dabigatran effect or not.

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41. Managing Bleeding Complications

- No specific antidote for reversal of anticoagulant effect exists
- Management of hemorrhage with dabigatran consists predominantly of supportive measures

For Minor Bleeding (e.g., recurrent epistaxis)

- May be managed as outpatient
- Decision to hold or continue dabigatran will be based on clinical judgment and the balance of risks versus benefits
- Assess for drug compliance (e.g., ensure that extra doses were not consumed)
- Assess for change in renal function (serum creatinine)
- Evaluate for anatomical abnormalities that may explain epistaxis

For Major Bleeding (e.g., gastrointestinal, hematuria or hemodynamic instability)

General measures

- Hold dabigatran
- Consider hospitalization; obtain typical laboratory assays (e.g., CBC, PT, APTT)
- Pay close attention to hemodynamic stability with appropriate resuscitation measures (e.g., intensive care unit admission, pressors, adequate IV access)
- Evaluate for anatomical defects that may explain hemorrhage (e.g., GI ulcers that may be amenable to endoscopic control)
- A health care team may need to be mobilized (e.g., GI, surgery, radiology)

Specific measures

- If dabigatran was consumed within two hours of presentation, administer activated charcoal at standard doses (*van Ryn, 2009 [R]*).
- Empiric transfusion of fresh frozen plasma is not advised (the prolonged clotting times are a reflection of thrombin [factor II] inhibition and not a clotting factor deficiency).
- Replace packed RBCs as indicated.
- Hemodialysis is the only known effective intervention that reduces plasma dabigatran concentration. Approximately 70% of dabigatran is removed after four hours dialysis (*Stangier, 2010 [B]*; *Stangier, 2008 [A]*).

NOTE: the dabigatran volume of distribution is 50-70 L, and a rebound increase in plasma levels of dabigatran may occur after hemodialysis.

- As a last resort, consider use of procoagulant hemostatic agents such as recombinant factor VIIa or prothrombin complex concentrates, which have been shown to shorten clotting times in vitro and in the rat model. However, they did not reduce blood loss in the rat model, and there are no data on clinical efficacy of control of bleeding in humans (*van Ryn, 2008 [R]*).

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42. Perioperative Management

Pre-Procedure Management

- The time interval between discontinuing dabigatran and surgical intervention is based on the risk of bleeding and the patient's renal function. This time interval will be longer in individuals with decreased renal function.
- Procedures considered to have a high bleeding risk include cardiac surgery, neurosurgery, abdominal surgery, spinal anesthesia and surgeries involving major organs. Additional determinants of bleeding risk include advanced age, comorbidities and concomitant use of antiplatelet therapy.
- In patients with normal renal function (creatinine clearance >50 mL/min), discontinue dabigatran at least 24 hours prior to the procedure. However, for patients undergoing an intervention considered to have a high risk for bleeding, dabigatran should be discontinued 2 to 4 days prior to the intervention.
- For patients with estimated creatinine clearance between 30 to 50 mL/min, dabigatran should be discontinued at least 48 hours before the procedure; for high bleeding risk situations, dabigatran should be discontinued at least four days before the procedure.
- For patients with estimated creatinine clearance less than 30 mL/min, dabigatran should be discontinued for at least five days or longer.
- In patients at high risk of bleeding, a Thrombin Time (TT) can be performed 6-12 hours prior to surgery. A normal TT indicates that no drug is present (*van Ryn, 2010 [R]*). However, the TT does not accurately reflect plasma dabigatran concentrations, so it is not useful in providing an estimate of risk for surgical hemorrhage.

Post-Procedure Management

- It should be noted that, unlike warfarin, the anticoagulant effect of dabigatran occurs within one hour (if taken on an empty stomach), or three hours (if taken with a meal) after drug ingestion (*Medical Letter, The, 2010 [NA]*).
- Timing of resumption of dabigatran after the procedure needs to be tailored to the procedure and its postoperative bleed risk.

Bridging for Warfarin Patients

At present, there is no experience with the use of dabigatran as a bridging agent (to replace heparin products) for patients on chronic warfarin therapy undergoing procedures. Because of its effect on the INR, dabigatran could potentially interfere with the use of flexible dosing protocols used to establish warfarin dosing during initiation. Heparin products are considered the preferred anticoagulants to use with warfarin during these circumstances.

Cardioversion

In a subgroup analysis of patients who underwent cardioversion while participating in the RE-LY trial, dabigatran had a low incidence of stroke and major bleeding within 30 days of cardioversion and was comparable to warfarin patients. Dabigatran was considered a safe alternative to warfarin in patients requiring cardioversion (*Nagarakanti, 2011 [A]*).

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43. Parenteral Direct Thrombin Inhibitors

Parenteral DTI's are presently approved for use in patients with active heparin-induced thrombocytopenia (HIT) and those with a previous history of HIT who require anticoagulation therapy.

Consultation with a hematologist or anticoagulation expert is done when using these new anticoagulant drugs because of both drug and disease complexities.

Argatroban

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 impairment.

Bivalirudin

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)

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.

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44. Contraindications

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

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45. 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

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46. Adverse Effects

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

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47. Pregnancy

- FDA Pregnancy Category B (Micromedex [last accessed on December 21, 2009]) (*Briggs, 2008 [R]*)

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48. Breastfeeding

- Likely compatible, no human data (*Briggs, 2008 [R]*)

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49. 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.

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50. Dosing

Testing should be obtained before initiation of direct thrombin inhibitors:

Complete blood count (CBC)/Platelet count

PT/INR

aPTT

Liver enzymes (ALT, AST, GGT)

Creatinine

Table 4: Treatment Options for HIT (With or Without Thrombosis)

Argatroban	Bivalirudin	Lepirudin
<ul style="list-style-type: none"> • Dose adjustment necessary in patients with hepatic impairment. • Patients with heart failure, multiple organ system failure and anasarca, as well as those in the immediate post-cardiac surgery period, should receive an lower initial infusion rate (<i>Warkentin, 2008a [R]</i>). • Dose adjusted to maintain aPTT at 1.5-3.0 times normal (not to exceed 100 seconds). 	<ul style="list-style-type: none"> • Dose adjustment necessary in patients with renal impairment. • Dose adjusted to maintain aPTT at 1.5-2.5 times normal. 	<ul style="list-style-type: none"> • Dose adjustment necessary in patients with renal impairment. • There are two dosing regimens available the FDA-approved dose and an alternate dose recommended by the CHEST guidelines (<i>Warkentin, 2008a [R]</i>). The alternate dosing regimen has been recommended due to higher rates of bleeding associated with the FDA-approved dosing. • The alternate dosing regimen recommends omitting the initial IV bolus unless there is perceived life-or limb-threatening thrombosis, where a reduced bolus dose is preferred. (<i>Warkentin, 2008a [R]</i>). • Dose adjusted to maintain aPTT at 1.5-2.5 times normal.

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51. Correction of Supratherapeutic Anticoagulation Caused by Parenteral 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]*)

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52. Key Patient Education Components

Importance of understanding aPTT and target ranges.

Know and watch for signs of bleeding.

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Antiplatelet Agents

53. 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.

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.

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

- **Thienopyridines (clopidogrel, prasugrel)**

Thienopyridines selectively block the ADP receptor PP2Y12, thus preventing ADP-induced platelet aggregation. Both clopidogrel and prasugrel are orally administered inactive prodrugs; after absorption, they are converted to their active metabolites by liver cytochrome (CYP) P450 complex of enzymes. Clopidogrel is converted by the CYP 2C19 and prasugrel by the CYP 3A4 and 2B6 enzymes. Conversion of clopidogrel by the CYP2C19 enzyme is dependent on the genotype of that enzyme.

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.

Drug interaction with proton pump inhibitors (PPI)

Proton pump inhibitors (PPIs), typically used in conjunction with antiplatelet agents such as clopidogrel to reduce gastrointestinal blood loss, result in reduced plasma concentrations of active metabolite of clopidogrel, thus lowering the antiplatelet effect of clopidogrel in vitro (*Gilard, 2008 [A]*). This interaction is due to competitive inhibition of the metabolism of clopidogrel by CYP2C19, which generates its active metabolite.

In November 2009 the FDA issued a statement advising prescribers that in patients taking clopidogrel, to avoid using selected PPIs (and other drugs – e.g., cimetidine, esomeprazole, fluoxetine, fluconazole, ketoconazole) that inhibit CYP2C19.

(<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm> last accessed February 1, 2011)

Though the FDA issued a boxed warning, post-hoc analysis of two studies (*Ray, 2010 [B]*; *O'Donoghue, 2009 [A]*) did not confirm these adverse cardiovascular outcomes. The ACC/AHA issued a statement that suggested that additional clinical studies are needed before a formal recommendation could be made (*Kushner, 2009 [R]*). Additional management guidelines, on this topic, are being prepared by the ACC/AHA.

The gastroprotective effects of PPIs were demonstrated in results from COGENT trial (*Bhatt, 2010 [A]*). In patients requiring dual antiplatelet therapy (clopidogrel and aspirin) the incidence of gastrointestinal (GI) hemorrhage in patients on omeprazole (1.1%) was reduced compared to patients on placebo (2.9% HR 0.34, 95% CI, 0.18 to 0.63; P<0.001). Although the rate of cardiovascular events in patients on omeprazole was not increased, this study was not powered to detect such a difference.

After a consensus-building discussion, the ICSI Antithrombotic work group recommends:

- Risks and benefits of concomitant clopidogrel and PPI use must be carefully evaluated and documented on an individual patient basis
- Discontinue PPI if there is no strong indication for one
- Consider H2 blockers (famotidine, nizatidine and ranitidine)
- Pantoprazole does not inhibit CYP2C19 and is a reasonable option. However, this has not been shown to be significant in clinical trials (*O'Donoghue, 2009 [A]*).

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CYP2C19 gene polymorphisms and clopidogrel effect

Polymorphisms (or variants or different alleles) of the CYP2C19 enzyme have been shown to affect metabolism of clopidogrel. Patients who have two normal metabolism alleles (also termed wild type, or CYP2C19*1) have fully functional normal metabolism. Patients with one loss-of-function allele (termed heterozygous carriers of CYP2C19*2) and those with two loss-of-function alleles (termed homozygous carriers of CYP2C19*2) have a reduced metabolism of clopidogrel.

The latter two groups of patients, with reduced metabolism of clopidogrel, have a suboptimal platelet inhibition that may result in increased cardiovascular morbidity and mortality compared to normal metabolizers. However, there are multiple non-genetic and genetic variables that affect platelet inhibition.

In March 2010 the FDA issued a new boxed warning to the product label of clopidogrel bisulfate (marketed as Plavix). The exact wording of the black box warning is as follows:

The effectiveness of clopidogrel hydrogen sulfate is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Clopidogrel hydrogen sulfate at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel hydrogen sulfate at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers (<http://products.sanofi-aventis.us/plavix/plavix.html>, accessed March 4, 2011).

Specifically, the purpose is to:

- warn about reduced effectiveness in patients who are poor metabolizers of clopidogrel – poor metabolizers do not effectively convert clopidogrel to its active form in the body; decreased responsiveness has been associated with worse outcomes in clinical trials.
- inform health care professionals that tests are available to identify genetic differences in CYP2C19 function, and platelet function testing.
- advise health care professionals to consider use of other anti-platelet medications or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers.

(<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm204256.htm>, last accessed February 14, 2011)

In response to the FDA warnings, the American College of Cardiology Foundation task force and American Heart Association have issued a joint statement pointing to the lack of definitive data to guide endorsement of a specific treatment strategy, noting that clinical trials are currently under way to help address the matter.

Another summary from ACCF/AHA issued in June of 2010 re-emphasized the above findings, and stated that the clinical outcomes of specific genetic polymorphisms is undetermined and the predictive value of pharmacogenomics and platelet function testing is unknown.

There is insufficient information to recommend either routine genetic or platelet function testing at this time, and there is no randomized data to suggest testing improves outcomes. Clinical judgment should be used to assess clinical risk, and genetic testing may be considered in individuals thought to be high risk.

Pending availability of evidence-based guidelines, practical patient management suggestions have been made (*Holmes, 2010 [R]*).

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Key messages from this statement include:

- Residual platelet reactivity in patients receiving clopidogrel is associated with increase risk of cardiac and cerebrovascular and peripheral arterial events.
- This variability, due to pharmacokinetic and pharmacodynamic factors, is due to multiple factors including variables such as increased age, body mass index, comorbidities such as diabetes and dyslipidemia. Genetic variability likely explains only a small proportion of this variation.
- Genetic testing for CYP2C19 (pharmacogenetic testing) is not widely available, in addition, generally test turnaround times preclude applicability of the information for acute phases of patient care.
- Point-of-care testing for the CYP2C19 is not yet available.
- Costs of these tests are typically not reimbursed by major payers.

In spite of limitations in available data, some practical recommendations for practice were provided:

- Adherence to the existing ACCF/AHA guidelines for use and a platelet therapy should remain the foundation for practice.
- The predicted value of pharmacogenetic testing is limited and is a focus of multiple ongoing clinical studies.
- The evidence for routine pharmacogenetic testing is insufficient, however, in patients felt to be at moderate or high risk for poor outcomes (patients undergoing elective high-risk PCI procedures or treatment of extensive or complex disease), pharmacogenetic testing may be considered with alternative therapy (e.g., prasugrel) in patients predicted to be poor metabolizers.
- For patients experiencing recurrent thrombosis despite clopidogrel, options include increasing the dose of clopidogrel or consideration of alternatives such as prasugrel.

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.

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Antiplatelet Agents – Oral

54. Contraindications

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

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55. 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

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56. Adverse Effects

Combination of aspirin and clopidogrel and/or combination with warfarin or other anticoagulant has 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

Thienopyridines (clopidogrel, prasugrel)

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

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57. Pregnancy

Third-trimester risks of placental separation and hemorrhage (*Caritis, 1998 [A]*). FDA class D positive evidence of human fetal risk. Maternal benefit may outweigh fetal risk in serious or life-threatening situations.

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58. Breastfeeding

FDA class Possibly Unsafe: Available animal or human data demonstrates potential or actual adverse effects to infants. Consider alternatives or weigh risks and benefits. Some community practice reflects use of 81 mg ASA daily as antiplatelet therapy.

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59. 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, and
- fecal blood testing.

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60. Dosing

Aspirin

For all clinically important end point events, oral doses ranging between 81 and 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 of 300-600 mg (*Von Beckerath, 2005 [A]; Savcic, 1999 [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.

Prasugrel

Prasugrel is FDA approved for acute coronary syndrome in patients undergoing percutaneous coronary intervention (PCI). The recommended loading dose is 60 mg x1, followed by a maintenance dose of 10 mg once daily. Patients should also take concomitant aspirin 75-325 mg once daily.

Prasugrel and clopidogrel were compared head to head in the TRITON-TIMI 38 trial. This trial included 13,608 patients with moderate- to high-risk acute coronary syndrome with scheduled PCI. Patients were randomized to receive prasugrel (60 mg loading dose and 10 mg once-daily maintenance dose) or clopidogrel (300 mg loading dose and 75 mg once-daily maintenance dose) for 6-15 months. The primary end point was death from cardiovascular causes, non-fatal myocardial infarction (MI) or non-fatal stroke. The primary safety end point was bleeding. Prasugrel was found to be more effective than clopidogrel at reducing the primary end point (12.1% vs 9.9%, HR, 0.81; 95% CI 0.73-0.90; p<0.001). However, prasugrel had a

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greater incidence of life-threatening bleeding (1.4% vs 0.9%, HR, 1.32; 95% CI 1.03-1.68; p=0.03) (Wiviott, 2007 [A]).

Prasugrel has a FDA black box warning regarding bleeding risk, and patient selection is important.

Candidates for prasugrel should meet the following criteria:

- Acute coronary syndrome managed by PCI
- Receiving adjunct aspirin therapy
- Not undergoing CABG
- < 75 years old
- Weight ≥ 60 kg
- No history of TIA/stroke or bleeding predisposition

(Wiviott, 2007 [A])

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 end points 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 end points, 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 (versus ASA alone), but still unacceptable in the absence of benefit (Bhatt, 2006 [A]).

Dipyridamole

Antiplatelet oral dose 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]).

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61. Combination Antiplatelet Therapy

Combined antiplatelet therapy has been used in acute coronary syndrome (ACS) for some time and proven to be effective (Yusuf, 2001 [A]).

Two clinical studies have addressed the effectiveness of combined aspirin with clopidogrel for prevention of stroke in atrial fibrillation (Connolly, 2009 [A]; ACTIVE Writing Group, The, 2006 [A]). ACTIVE A compared aspirin with combined aspirin and clopidogrel in patients who were considered to be poor candidates for warfarin therapy. This showed that the combination reduced incidence of both stroke (2.4% vs. 3.3. %) and myocardial infarction (0.2% vs. 0.9%), but increased risk of major hemorrhage from 1.3% to 2.0% per year, compared to aspirin alone. In the ACTIVE W study, warfarin was significantly better than combined ASA/clopidogrel therapy in the prevention of embolic stroke.

In patients with atrial fibrillation, providers should carefully select use of warfarin versus aspirin (with or without clopidogrel), based on the relative risk of stroke versus the overall risk of hemorrhage using these therapies (Connolly, 2009 [A]; ACTIVE Writing Group, The, 2006 [A]).

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62. Treatment of Bleeding Caused by Oral Antiplatelet Agents

Platelet infusion.

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63. 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.

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Antiplatelet Agents – Parenteral

64. 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

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65. 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 are achieved.
- Patients should be maintained on adequate bed rest following sheath removal or discontinuation of IIB/IIIA inhibitors.
- Thrombocytopenia has been observed; platelet counts should be monitored.

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66. Adverse Effects

Major bleeding.

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

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67. Pregnancy

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

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68. Breastfeeding

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

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69. 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, and
- fecal blood testing.

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70. 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

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71. Treatment of Bleeding Caused by Parenteral Antiplatelet Agents

Platelet infusion.

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72. 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.

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Mechanical Heart Valves in Patients Who Are Pregnant

73. 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.

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Perioperative Management

74. Anticoagulation Bridging

Interruption of chronic warfarin therapy is occasionally needed when patients undergo procedures. To achieve adequate hemostasis, warfarin is held for 4-5 doses (depending on patients INR range) prior to procedure. Warfarin is then restarted immediately following the procedure but does not achieve an adequate anticoagulation effect for at least 5 days. Therefore, patients who hold warfarin therapy for procedures have a 7-10 day period where they are not receiving antithrombotic protection from warfarin. Depending on the patient's circumstances, a decision is sometimes made to "bridge" this interval off warfarin with a shorter-acting parenteral anticoagulant such as IV UFH or LMWH. However, bridge therapy can increase the patient's risk of procedure-related bleeding, especially when given immediately after the procedure. The decision to use short-acting parenteral anticoagulants or simply hold warfarin without bridging takes into account the individual patient's risk of a thrombotic event off warfarin weighed against his/her risk of bleeding complications from the procedure and parenteral anticoagulants. The table below gives examples of cardiac conditions with variable risks of thromboembolic events.

Table 5. 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 (bi-leaflet – St. Jude/Medtronic Hall)	4-10
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])

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Algorithm Annotations

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 his/her 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]). Table 5 lists low-risk bleed procedures (Ansell, 2008 [R]).

Table 6. Low Bleeding Risk Procedures That Can Be Performed Without Discontinuing Warfarin

Dental	Dermatologic	Gastrointestinal	Ophthalmic
Endodontics	Mohs' surgery	Biliary stent without sphincterotomy	Cataract surgery
Periodontal therapy	Simple excisions	Colonoscopy without biopsy	Trabeculectomy
Prosthetics	Skin biopsy	Diagnostic endoscopic retrograde cholangiopancreatography	
Restorations		Diagnostic esophagogastroduodenoscopy	
Teeth cleaning		Endoscopic ultrasonography without biopsy	
Uncomplicated extractions		Push enteroscopy	

Thrombotic Risk Stratification

The ACCP has generated a grid, shown in Table 7, to help define the relative risk of thromboembolism in patients with different criteria for anticoagulation. This may be used as a guide for decision-making when determining when patients might warrant bridging with parenteral anticoagulation versus holding warfarin therapy.

Table 7. ACCP's Perioperative Thromboembolism Risk Stratification *

ACCP's suggested risk stratification for perioperative thromboembolism*			
Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (10%/yr risk of ATE or > 10%/mo risk of VTE)	Any mechanical mitral valve Older aortic valve Recent (< 6 mo) stroke or TIA	CHADS ₂ score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo) VTE Severe thrombophilia
Moderate (4%-10%/yr risk of ATE or 4%-10%/mo risk of VTE)	Bileaflet aortic valve and one of the following: atrial fibrillation, prior stroke/TIA, hypertension, diabetes, heart failure, age > 75 yr	CHADS ₂ score of 3 or 4	VTE within past 3-12 mo Recurrent VTE Nonsevere thrombophilic conditions Active cancer
Low (< 4%/yr risk of ATE or >2%/mo risk of VTE)	Bileaflet aortic valve without atrial fibrillation and no other risk factors for stroke	CHADS ₂ score of 0-2 (and no prior stroke or TIA)	Single VTE within past 3-12 mo and no other risk factors

* Reproduced, with permission of American College of Chest Physicians, from *Chest* (Douketis et al. The perioperative management of antithrombotic therapy. *Chest* 2008;133(suppl):299S-339S), copyright © 2008.
ACCP = American College of Chest Physicians; ATE = atrial thromboembolism; VTE = venous thromboembolism; TIA = transient ischemic attack

Algorithm Annotations

The CHADS₂ score ranges from 0 to 6 and is based on whether any of five risk factors are present. There is one point for each risk factor: congestive heart failure, hypertension and diabetes, age > 75 years, and two points for prior stroke or transient ischemic attack (*Douketis, 2008 [R]*).

Options for Anticoagulation Management Around the Time of Procedures

A summary of options for patients on anticoagulation to consider at the time of procedure is listed in Table 8. Clinicians should use their judgment and patient preferences in determining a final course of action.

Table 8. Perioperative Anticoagulation Management

		Patient Bleeding Risk for Procedure	
		Low	High
Patient Thromboembolic Risk	Low	Continue warfarin	Hold warfarin 5 days (4 doses) prior to procedure Restart day of procedure
	Moderate	Continue warfarin	Hold warfarin 5 days (4 doses) prior to procedure Consider parenteral anticoagulant bridge (LMWH or UFH) - If cardio embolic risk, use therapeutic dosing - If VTE risk, use prophylactic dosing
	High	Continue warfarin	Parenteral anticoagulant bridging (LMWH or UFH), therapeutic dosing

(*Jaffer, 2009 [R]; Douketis, 2008 [R]*)

Timing of Anticoagulation Management for Procedures

An example of a bridge protocol for patients receiving therapeutic parenteral anticoagulation therapy is shown in Table 9. Please be aware that studies have shown a significant risk for bleeding associated with therapeutic parenteral anticoagulation bridging. Patients should be made aware of both the thrombotic and bleeding risks associated with this approach and be involved in the final decision on bridging. There are no FDA-approved schedules for bridging.

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Table 9: Recommended Bridging Schedule

Days before Procedure	Warfarin	INR	Full-Dose (Therapeutic)* LMWH** or Therapeutic UFH
5 days prior to procedure	Last dose	Check if not done within two weeks prior	4-5 doses before procedure, start after first missed warfarin dose if at very high risk of thrombosis
4 days prior to procedure	None	None	4-5 doses 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.	LMWH – last dose 24 hours prior to surgery UFH IV – last dose 5 hours prior to surgery UFH SubQ – last dose 4 hours prior to 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.

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75. Perioperative Management of Antiplatelet Agents

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

- Clopidogrel and prasugrel seven days prior to surgery

Algorithm Annotations

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

Patients with recent coronary stenting may have significant risk of stent thrombosis if antiplatelet therapy is interrupted. Consultation with a cardiologist is recommended to determine the best course of action in these patients (*Jaffer, 2009 [R]*).

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76. Neuraxial Blockade Management (Spinal/Epidural)

Table 10a. 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 contraindications – but may enhance the anticoagulant and/or antiplatelet effects of other medications

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Table 10b. 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.

Algorithm Annotations

New challenges in the management of the anticoagulated patient undergoing neuraxial blockade have arisen as medical standards for the prevention of perioperative venous thromboembolism have been 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 pharmacodynamics 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. Vandermuellen (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 (*Geerts, 2004 [R]; Burnett, 1998 [R]; Lumpkin, 1998 [NA]; Horlocker, 1997 [R]*).

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 warfarin 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 ; Wu, 2001 [R]; Thompson, 1999 [R]*).

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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 have 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 (*Lumpkin, 1998 [NA]*; *Wysowski, 1998 [NA]*; *Horlocker, 1997 [R]*; *Vandermeulen, 1994 [R]*).

Newer anticoagulant drugs

The use of the newer factor Xa inhibitor, fondaparinux, or the thrombin inhibitors related to hirudin, 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, clopidogrel and prasugrel) 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.

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- 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 eptifibatid 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.

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77. 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.

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

The subdivisions of this section are:

- Resources
- Resources Table

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Resources

Criteria for Selecting Resources

The following resources were selected by the 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 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 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.

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Resources Table

*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	American College of Chest Physicians	ACCP Consensus Conference guidelines supporting anticoagulation clinics.	Providers	American College of Chest Physicians. Eighth ACCP Consensus Conference on Antithrombotic Therapy. <i>Chest</i> September 2008 Supplement. 1-800-343-2227
	American Medical Association 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 Society of Hematology (ASH)	The "Practice" area of the Web site provides "HIT Quick Reference" pocket guide that summarizes the diagnosis and treatment of heparin-induced thrombocytopenia.	Health Care Professionals	http://www.hematology.org/Practice/
	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
	Care Clinical Research	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.net
	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

* Available to ICSI members only.

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*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	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
	KRAMES Communications® 1998	If You Take Coumadin® Vitamin K Food list, a single sheet describing importance of diet, helpful hints and when to call the doctor.		https://shop.krames.com/
*	Mayo Clinic	"Oral Anticoagulant Therapy: Warfarin©" 2008 Mayo Foundation (MFMER), a 28-page patient education handout addressing basics about clotting and anticoagulants, therapy, includes daily INR/dosing diary for patient to keep records.	Health Care Professionals; Patients and Families	Available only upon request by ICSI member organization.
	Mayo Clinic	Patient education page on what is important prior to taking warfarin orally.	"Warfarin (Oral Route) Before Using"	http://www.mayoclinic.com/health/drug-information/DR602425/DSECTION=before%2Dusing
	Mayo Clinic	Patient education page on what is the proper use of warfarin.	"Warfarin (Oral Route) Proper Use"	http://www.mayoclinic.com/health/drug-information/DR602425/DSECTION=proper%2Duse
	Mayo Clinic	Patient education page on precautions to consider when taking warfarin orally.	"Warfarin (Oral Route) Precautions"	http://www.mayoclinic.com/health/drug-information/DR602425/DSECTION=precautions%2D
	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://stopthecлот.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

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*	Author/Organization	Title/Description	Audience	Web Sites/Order Information
	National Institutes 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.

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The subdivisions of this section are:

- References
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Links are provided for those new references added to this edition (author name is highlighted in blue).

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Appendix A – Risk Factors for Bleeding During Warfarin Therapy

Note: Many risk factors for bleeding are also risk factors for stroke.

Significant Variables to Predict Major Bleeding Events

- Age (> 70 years)
- Female gender
- Recent bleeding event
- Remote bleeding event
- Alcohol/drug abuse
- Diabetes
- Anemia (hematocrit < 30%)
- Concomitant antiplatelet therapy

A host of risk factors for bleeding events have been identified in the literature. In general, these risk factors can be grouped into:

- Demographics (age, gender, and nursing facility residence)
- Concomitant diseases (anemia, cancer, stroke, transient ischemic attacks, MI, hypertension, heart failure/cardiomyopathy, ischemic heart disease, diabetes, hepatic failure or peptic ulcer disease)
- Concomitant risks for injury (risk for falls, cognitive impairment, or surgery during hospitalization)
- **Additional Anticoagulation Treatment-Related Risk Factors**

Duration increased risk during initial three months of treatment, cumulative risk over time

Intensity INR greater than 4.0 per warfarin package insert

Variability of control adequacy of education, support, monitoring and follow-up

For patients who are otherwise deemed safe for outpatient warfarin therapy, the risk factors noted 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. Clinicians must weigh the potential benefits against each individual patient's risk for major bleeding.

(Lip, 2011 [NA], Shireman, 2006 [R])

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ICSI Document Development and Revision Process

Overview

Since 1993, the Institute for Clinical Systems Improvement (ICSI) has developed more than 60 evidence-based health care documents that support best practices for the prevention, diagnosis, treatment or management of a given symptom, disease or condition for patients.

Document Development and Revision Process

The development process is based on a number of long-proven approaches. ICSI staff first conducts a literature search to identify pertinent clinical trials, meta-analysis, systematic reviews, regulatory statements and other professional guidelines. The literature is reviewed and graded based on the ICSI Evidence Grading System.

ICSI facilitators identify gaps between current and optimal practices. The work group uses this information to develop or revise the clinical flow and algorithm, drafting of annotations and identification of the literature citations. ICSI staff reviews existing regulatory and standard measures and drafts outcome and process measures for work group consideration. The work group gives consideration to the importance of changing systems and physician behavior so that outcomes such as health status, patient and provider satisfaction, and cost/utilization are maximized.

Medical groups, who are members of ICSI, review each guideline as part of the revision process. The medical groups provide feedback on new literature, identify areas needing clarification, offer recommended changes, outline successful implementation strategies and list barriers to implementation. A summary of the feedback from all medical groups is provided to the guideline work group for use in the revision of the guideline.

Implementation Recommendations and Measures

Each guideline includes implementation strategies related to key clinical recommendations. In addition, ICSI offers guideline-derived measures. Assisted by measurement consultants on the guideline development work group, ICSI's measures flow from each guideline's clinical recommendations and implementation strategies. Most regulatory and publicly reported measures are included but, more importantly, measures are recommended to assist medical groups with implementation; thus, both process and outcomes measures are offered.

Document Revision Cycle

Scientific documents are revised every 12-24 months as indicated by changes in clinical practice and literature. Each ICSI staff monitors major peer-reviewed journals every month for the guidelines for which they are responsible. Work group members are also asked to provide any pertinent literature through check-ins with the work group mid-cycle and annually to determine if there have been changes in the evidence significant enough to warrant document revision earlier than scheduled. This process complements the exhaustive literature search that is done on the subject prior to development of the first version of a guideline.

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