ICSI

INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:
Venous Thromboembolism Prophylaxis

Fourth Edition
June/2007

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

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

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

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

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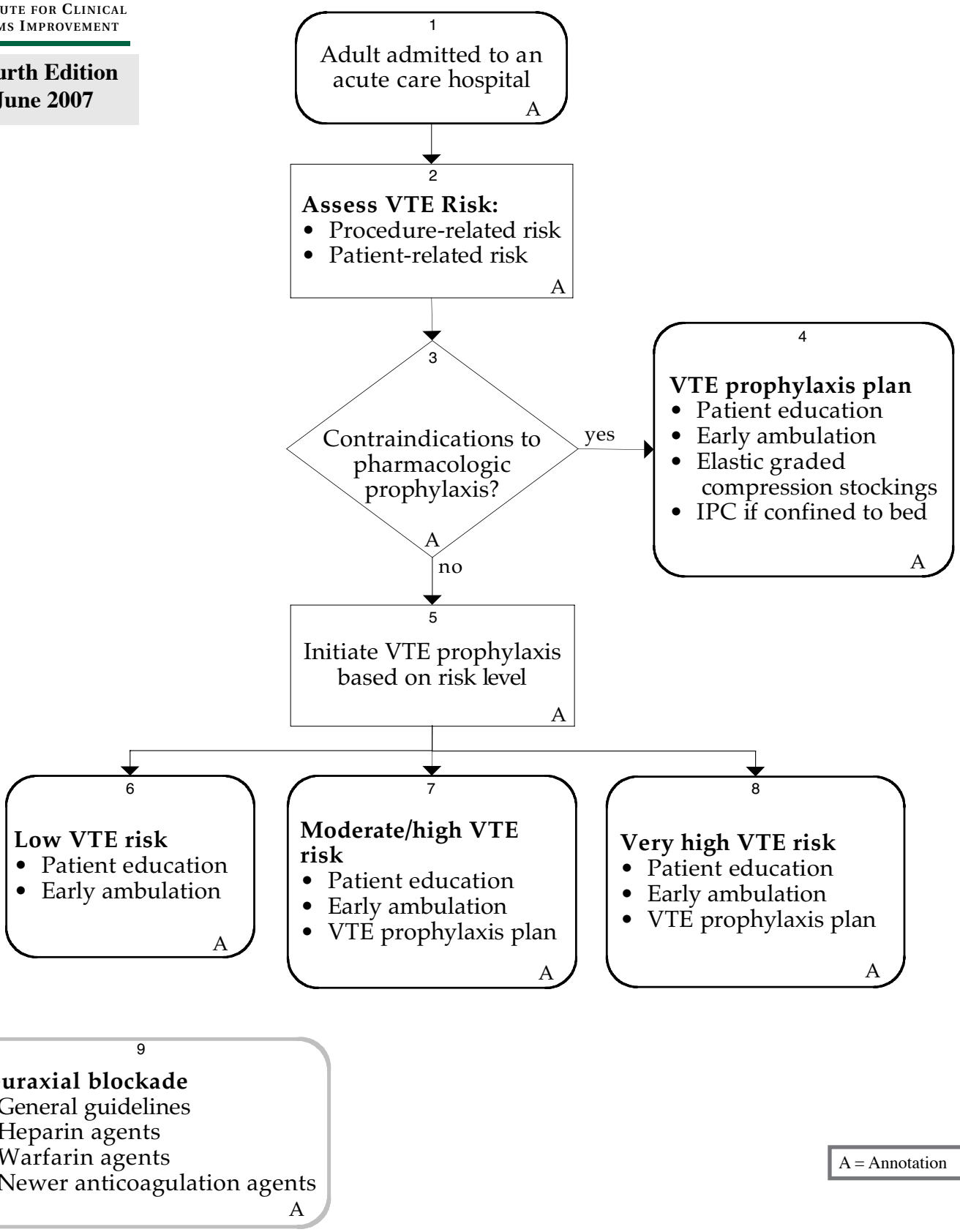

A = Annotation

VTE Prophylaxis Plan Table

	LMWH (Dalteparin or Enoxaparin)	Fondaparinux	UFH	Warfarin	GCS/IPC (Not TEDS)	Duration of Prophylaxis
Orthopedic Hip Replacement	Yes	Yes	No	Yes	Yes	Minimum 10 days post-op Consider 28-35 days post-op
Hip Fracture	Yes	Yes	No	Yes	Yes	Minimum 10 days post-op Consider 28-35 days post-op
Knee Replacement	Yes	Yes	No	Yes	Yes	Minimum 10 days post-op
Multiple Trauma	Yes	No	No	Yes	Yes	Until discharge unless there is impaired mobility
Spinal Cord Injury	Yes	No	No	No	Yes	Continue through rehabilitation phase
Elective Spine Surgery	Yes	No	Yes	No	If Immobile	
Neurosurgery	Yes	No	Yes	No	If Immobile	
Oncology Surgery *(Patients with active cancer are at the very highest risk for thrombolic events)*	Yes	Yes	Yes	Yes	Yes	
General Surgery Low Risk	No	No	No	No	If Immobile	
Moderate Risk	Yes	No	Yes	No	If Immobile	Until ambulatory
High Risk	Yes	No	Yes	No	If Immobile	Until discharge
Very High Risk	Yes	No	Yes	No	Yes	2-4 weeks after discharge
Gynecologic Surgery • Including Caesarean Section	Yes	No	Yes	No	If Immobile	
Urologic Surgery	Yes	No	Yes	No	If Immobile	
Medical Patients Low and Moderate Risk	Yes	No	No	Yes	Yes	
High and Very High Risk • Including ICU	Yes	Yes	Yes	Yes	Yes	Consider extending after discharge if there is impaired immobility

Key:
Yes – Prophylaxis treatment options that are recommended
No – Prophylaxis treatment options not recommended

Additional patient-related risk factors may place younger patients and/or those with more minor procedures into a higher-risk category. (See Annotation #2 for more information.) *(Grady, 2000; Hansson, 1999; Rosendaal, 1999)*

Supportive statements for pharmacotherapy of High-VTE-Risk patients:

1. For most general surgery patients, UFH remains the agent of choice. LMWH has been found to be as safe and effective, yet remains significantly more expensive *(Bergqvist, 2002; Kakkar, 1993; Mismetti, 2000)*.
2. In general surgery, patients may receive preoperative heparin without increased risk of bleeding *(Bjerkeset, 2000)*.
3. LMWHs cause less heparin-induced thrombocytopenia (HIT) than UFH. There is early evidence to support the use of fondaparinux in HIT, although further confirmatory studies are needed.

4. LMWH should be adjusted to prophylactic doses for patients with a creatinine clearance less than 30 mL/min *(Sanderink, 2002)*. The manufacturer-recommended dose of enoxaparin is 30 mg daily in this population; the manufacturer of dalteparin does not list a similar dose recommendation.

5. Fixed-dose prophylaxis in the severely obese patient will likely result in underdosing. Current expert opinion suggests that LMWH be increased by 25% in the very obese patient (BMI 35 or more): for example, enoxaparin 40 mg every 12 hours.

6. In gynecologic surgery, evidence is strongest to support use of UFH. For patients with malignancy, a regimen of every-eight-hours dosing should be maintained *(Geerts, 2004)*.

Supportive comments for pharmacotherapy of patients at Very High VTE Risk:

1. Warfarin is contraindicated in the first trimester of pregnancy. Refer to the ICSI Anticoagulation Therapy Supplement for further dosing information.

2. Warfarin (INR 2.0-3.0) alone without concomitant heparin has been shown effective in prevention of venous thromboembolism for patients requiring hip replacement surgery or elective knee arthroplasty *(Geerts, 2004)*.

3. Warfarin may be used when the patient has a history of heparin-induced thrombocytopenia (HIT).

4. LMWHs cause less heparin-induced thrombocytopenia (HIT) than LDUH. There is early evidence to support the use of fondaparinux in HIT, although further confirmatory studies are needed.

5. LMWH should be adjusted to prophylactic doses for patients with a creatinine clearance less than 30 ml/min *(Sanderink, 2002)*. The manufacturer-recommended dose of enoxaparin is 30 mg daily in this population; the manufacturer of dalteparin does not list a similar dose recommendation.

6. Fixed-dose prophylaxis in the severely obese patient will likely result in underdosing. Current expert opinion suggests that LMWH be increased by 25% in the very obese patient (BMI 35 or more): for example, enoxaparin 40 mg every 12 hours.

7. In patients who have undergone total knee replacement (TKR), total hip replacement (THR) and hip fracture repair, a minimum of 10 days of anticoagulation prophylaxis is recommended. For patients undergoing THR or hip fracture repair, extending prophylaxis to 28-35 days of post-op anticoagulation should be considered. See above chart for recommended agents.

8. Dalteparin and enoxaparin are started 12-24 hours post-op depending on physician determination of adequate hemostasis.

9. Fondaparinux is the only anticoagulant with an FDA-approved indication for hip fracture *(Bauer, 2001; Eriksson, 2001; Lassen, 2002; Turpie, 2002)*.

10. UFH is not recommended for very high-risk patients.

11. For trauma patients, contraindications to early pharmacotherapy include intracranial bleeding, incomplete spinal cord injury, ongoing, uncontrolled bleeding and uncorrected coagulopathy.

Table of Contents

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Foreword

Scope and Target Population

This guideline addresses risk assessment for venous thromboembolism (VTE), risk assessment for bleeding, and mechanical and pharmacologic therapies to reduce the occurrence of VTE in adult hospitalized patients.

Clinical Highlights and Recommendations

- All patients should be evaluated for VTE risk upon hospital admission, change in level or care, change in providers, and prior to discharge. *(Annotations #1, 2)*
- All patients should receive proper education regarding VTE risk, signs and symptoms of VTE, and prophylaxis methods available. *(Annotations #4, 5, 6, 7, 8)*
- Early and frequent ambulation should be encouraged when possible in all patient groups. *(Annotations #4, 5, 6, 7, 8)*
- Risk of VTE development continues beyond hospitalization, and the need for postdischarge anticoagulation should be assessed. *(Annotations #7, 8)*
- All surgical/trauma patients who have moderate/high or very high risks for VTE should receive anticoagulation prophylaxis unless contraindicated. *(Annotations #7, 8)*
- All medical patients who have a high risk for VTE should receive anticoagulation prophylaxis unless contraindicated. *(Annotations #7, 8)*
- Aspirin is not recommended for routine VTE prophylaxis following hip/knee arthroplasty but may be considered in some circumstances. Further study is needed. *(Annotation #8)*
- Aspirin and antiplatelet drugs are not recommended for VTE prophylaxis in other surgical patients or medically ill patients. *(Annotations #7, 8)*
- For all patients receiving spinal or epidural anesthesia, precautions should be taken when using anticoagulant prophylaxis to reduce the risk of epidural hematoma. *(Annotation #9)*

Priority Aims

1. Increase the percentage of hospitalized adult patients (18 years and older) who are appropriately assessed for VTE risk within 24 hours of admission. *(Annotations #1, 2) (JCAHO/CMS Quality Measure)*
2. Increase the percentage of patients who are assessed for VTE risk upon change in level of care, change in providers, and/or upon discharge. *(Annotation #2)*
3. Increase the percentage of hospitalized adult patients (18 years and older) who are at risk for VTE who have received education for VTE that includes VTE risk signs and symptoms, and treatment/prophylaxis methods available within 24 hours of admission. *(Annotations #4, 5, 6, 7, 8) (JCAHO/CMS Quality Measure)*
4. Increase the percentage of hospitalized adult patients who begin early and frequent ambulation to reduce VTE risk. *(Annotations #4, 5, 6, 7)*

5. Increase the percentage of hospitalized adult patients (18 years and older) receiving appropriate pharmacological and/or mechanical prophylaxis treatment within 24 hours of admission. *(Annotations #7, 8)*
6. Reduce the risk of complications from pharmacologic prophylaxis. *(Annotations #3, 7, 8, 9) (JCAHO/ CMS Quality Measure)*
7. Increase the percentage of patients who are discharged on warfarin who have an international normalized ratio (INR) within one week. *(Annotations #7, 8)*

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Medical groups and hospitals are encouraged to develop a formal strategy that addresses the prevention of thromboembolic complications.
   - Develop organization-specific protocols.
   - Develop documents outlining the operational steps taken when formalizing strategies around prevention of thromboembolic complications.
2. Medical groups and hospitals are encouraged to develop systems that support:
   - early identification of patients at risk for VTE development (possibly through use of order sets or similar tools);
   - appropriate prophylaxis initiation (possibly through order sets and/or anticoagulation and ambulation protocols); and
   - patient education to include documentation of the patient's own awareness of their risk for VTE, signs and symptoms of VTE and when/how to seek treatment, and demonstrated understanding of the prescribed anticoagulation regimen.

Related ICSI Scientific Documents

Related Guidelines

- Anticoagulation Therapy Supplement
- Heart Failure in Adults
- Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome (ACS)
- Diagnosis and Initial Treatment of Ischemic Stroke
- Venous Thromboembolism

Order Sets

- Admission for Ischemic Stroke for Patients Not Receiving tPA
- Admission to CCU for Acute Coronary Syndrome
- Admission for Heart Failure
- Discharge for Heart Failure
- ER Orders for Heart Failure

- Preoperative Total Hip and Total Knee Arthroplasty
- Postoperative Total Hip and Total Knee Arthroplasty
- Prevention of Ventilator-Associated Pneumonia

Patient and Family Guidelines

- Heart Failure in Adults

Disclosure of Potential Conflict of Interest

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

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

ICSI's conflict of interest policy and procedures are available for review on ICSI's Web site at http://www.icsi.org.

Introduction to ICSI Document Development

Each guideline, order set and protocol is developed by a 6- to 12-member work group that includes physicians, nurses, pharmacists and other health care professionals relevant to the topic, along with an ICSI staff facilitator. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, one or two members may be recruited from medical groups or hospitals outside of ICSI.

Prospective work group members are asked to disclose any potential conflicts of interest relevant to the topic of the document; disclosure forms are reviewed for unacceptable conflicts. At the beginning of each work group meeting, the potential conflicts of interest that have been disclosed are reviewed by the work group.

The work group meets for seven to eight three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

Critical Review Process

The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes needed across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within ICSI.

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Approval

Each guideline, order set and protocol is approved by the appropriate steering committee. There is one steering committee each for Respiratory, Cardiovascular, Womens' Health and Preventive Services. The Committee for Evidence-Based Practice approves guidelines, order sets and protocols not associated with a particular category. The steering committees reviews and approves each guideline based on the following:

- Member comments have been addressed reasonably.
- There is consensus among all ICSI member organizations on the content of the document.
- To the extent of the knowledge of the reviewer, the scientific recommendations within the document are current.
- Either a critical review has been carried out, or to the extent of the knowledge of the reviewer, the changes proposed are sufficiently familiar and sufficiently agreed upon by the users that a new round of critical review is not needed.

Once the guideline, order set or protocol has been approved, it is posted on the ICSI Web site and released to members for use. Guidelines, order sets and protocols are reviewed regularly and revised, if warranted.

Document Revision Process

ICSI scientific documents are revised every 12-36 months as indicated by changes in clinical practice and literature. Every six months, ICSI checks with the work group to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Prior to the work group convening to revise the document, ICSI members are asked to review the document and submit comments. During revision, a literature search of clinical trials, meta-analysis and systematic reviews is performed and reviewed by the work group. The work group meets for one to two three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

If there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations, it is sent to members to review prior to going to the appropriate steering committee for approval.

Evidence Grading System

A. Primary Reports of New Data Collection:

Class A: Randomized, controlled trial

Class B: Cohort study

Class C: Non-randomized trial with concurrent or historical controls
Case-control study
Study of sensitivity and specificity of a diagnostic test
Population-based descriptive study

Class D: Cross-sectional study
Case series
Case report

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

Class M: Meta-analysis
Systematic review
Decision analysis
Cost-effectiveness analysis

Class R: Consensus statement
Consensus report
Narrative review

Class X: Medical opinion

Algorithm Annotations

1. Adult Admitted to an Acute Care Hospital

The American College of Chest Physicians (ACCP) consensus recommends that all institutions develop a formal strategy that addresses the prevention of thromboembolic complications. This guideline is intended for patients who may have patient-related and/or procedure-related risk factors that increase the risk for venous thromboembolism (VTE).

Appropriate prophylactic measures should be utilized whenever possible to minimize these risks and lower overall morbidity and mortality associated with this disease.

Frequently encountered high-risk circumstances are best addressed with written protocols and order sets to standardize the care given to these types of patients.

2. Assess VTE Risk

Key Points:

- All patients should be assessed for VTE risk upon admission, change in level of care, change in providers, and/or upon discharge.
- Patients undergoing surgical procedures or suffering significant trauma are at risk for developing venous thromboembolism.
- Patients admitted for medical reasons should be evaluated for risk of VTE development.
- Appropriate prophylaxis measures should be initiated for patients based on risk for developing VTE.

Multiple studies have identified risk factors associated with VTE in hospitalized patients. Medical factors are considered to be contributory to surgical- and trauma-related factors, though the degree of increased risks to patients has not been well studied.

There is ample evidence to demonstrate that prophylactic measures such as anticoagulants and/or mechanical compression are a cost-effective method in VTE prevention. Despite this fact, there is also evidence that VTE prophylaxis is underutilized in the hospital setting. One study showed that only one third of 2,000 hospitalized patients received prophylaxis, despite multiple risk factors *(Geerts, 2004)*.

VTE Risk for Surgery without Prophylaxis

Level of Risk	Surgery	Age	Additional Risk Factors	Calf DVT	Proximal DVT	Clinical PE	Fatal PE
Low	Minor	Under 40	None	2%	0.4%	0.2%	0.002%
Moderate	Minor Non-Major Major	- 40-60 Under 40	Yes None None	10%-20%	2%-4%	1%-2%	0.1%-0.4%
High	Non-Major Non-Major Major Major	Over 60 Under 60 Over 40 Under 40	+/- Yes +/- Yes	20%-40%	4%-8%	2%-4%	0.4%-1.0%
Very High	Major (hip/knee arthroplasty, hip fracture, major trauma, spinal cord injury)	Over 40	Prior VTE, Active Thrombogenic Malignancy	40%-80%	10%-20%	4%-10%	0.2%-0.5%

Procedure-related risk

Venous thromboembolism is highly prevalent in hospitalized patients undergoing procedures or suffering significant trauma. Surveillance data collected from several studies show that the incidence of VTE by phlebography or fibrinogen scan uptake can be as high as 45%-50% in elective hip replacement, knee replacement, hip fracture and patients with multiple trauma. Venographic data suggest an incidence of 25%-35% in patients undergoing general, urologic and gynecologic surgery.

Though the incidence of clinically significant disease is less than venographic findings, patients can have as high as a 1.6%, 4%, or 6.9% risk of clinical pulmonary embolism with general surgery, elective hip replacement or traumatic orthopedic surgery respectively.

Salzman and Hirsh classified risk according to the presence of likelihood for VTE associated with patients who were not given prophylaxis. High-risk patients were those with a 40%-80% incidence of calf DVT on surveillance, 10%-30% risk of proximal DVT and greater than 1% incidence of fatal pulmonary embolism. Moderate-risk was 10%-40% calf DVT, 1%-10% proximal DVT and 0.1%-1% fatal pulmonary embolism. Low-risk patients were less than 10% calf DVT, less than 1% proximal DVT and less than 0.1% fatal pulmonary embolism. The ACCP consensus panel has further classified patients in low-, moderate-, high- and very high-risk categories.

Surveillance has been shown to be both expensive and too lacking in the appropriate sensitivity and specificity for asymptomatic patients to be an effective strategy in VTE prophylaxis.

(Geerts, 2004; Nicolaides, 2006)

Supporting evidence is of class: R

Patients undergoing surgical procedures have VTE risks associated with the procedure such as:

- site,
- surgical technique,
- duration,
- type of anesthesia,
- complications (infection, shock, etc.), and
- degree of immobilization.

Procedures that are considered high risk include:

- major open abdominal or urologic surgery,
- cranial and spinal neurosurgical procedures, and
- open gynecologic procedures.

Lower extremity joint replacement and hip fracture repair are considered very high VTE risk in themselves.

Patients with trauma have VTE risks dependent on location and severity. Patients with multisystem, spinal cord or lower extremity blunt trauma appear to be at very high risk.

(Geerts, 2004)

Patient-related risk

Other VTE risk factors that play an additive role include:

- Admission to the ICU
- Admission with an estimated length of stay four days or more
- Age
  - Low risk less than age 40
  - Moderate risk ages 40-60
  - High risk over age 60
- Cardiac dysfunction
  - Acute MI
  - Uncompensated heart failure*
- Cancer, myloproliferative disorders
- Infection, severe/systemic
  - Sepsis/SIRS (sytemic inflammatory response syndrome)
  - Pneumonia
  - Abdominal infection
  - Pyelonephritis
  - Complicated skin and soft tissue infection
- Inflammatory conditions
  - Inflammatory bowel disease
  - Collagen vascular disorder
- Mobility, decreased
  - Paralysis from stroke
  - Other causes

- Nephrotic syndrome
- Obesity
- Obstetrical/gynecological
  - Hormone therapy
  - Pregnancy
- Pulmonary disease, severe
  - Respiratory failure
  - Exacerbation of COPD (chronic obstructive pulmonary disease)
  - Severe pulmonary hypertension
  - Interstitial lung disease
  - Pneumonia
- Thrombophilia
  - Acquired
  - Congenital
- Thrombosis
  - Previous PE or DVT

*See Appendix A, "Heart Failure Classification" for information on the classifications of heart failure and the comparison to ACC/AHA 2001 staging.

Patient with an anticipated length of stay greater than or equal to four days are at increased risk for developing VTE *(Mismetti, 2001; Leizorovicz, 2004)*.

Obesity is considered an independent risk factor for VTE. Fixed-dose prophylaxis in the severely obese (e.g., BMI 35 or more) patient will likely result in underdosing; however, weight-based dosing may lead to overdosing because intravascular volume does not have a linear relationship to total body weight. There are a limited number of studies addressing the obesity VTE prophylaxis issue with relatively small numbers *(Nicholaides, 2006; Rochat, 2006)*.

See the ICSI Diagnosis and Treatment of Chest Pain and Acute Coronary Syndrome guideline for recommendations on prophylaxis for patients suspected of MI.

See the ICSI Diagnosis and Initial Treatment of Ischemic Stroke guideline for recommendations on prophylaxis for patients suspected of CVA.

Supporting evidence is of classes: A, M, R

3. Contraindications to Pharmacologic Prophylaxis?

Pharmacologic prophylaxis is not without risk; however, for short-term prophylactic anticoagulation there are relatively few conditions with excessive bleeding risk or other considerations that would contraindicate anticoagulation. The patient's risk for thrombosis needs to be balanced with their risk of bleeding. There is no substitute for critical assessment and judgment on the part of the clinician when considering the relative benefits and risks of prophylactic anticoagulation.

Contraindications for pharmacologic prophylaxis include:

a. active major, significant bleeding (e.g., cerebral hemorrhage);

b. extreme thrombocytopenia (less than 50,000 mm_3);

c. history of heparin-induced thrombocytopenia (HIT), contraindicated for use of heparins;

d. uncontrolled hypertension (systolic greater than 200, diastolic greater than 120);

e. bacterial endocarditis;

f. active hepatitis or hepatic insufficiency; and

g. other conditions that could increase the risk of bleeding.

Neuraxial blockade is not a contraindication for pharmacologic prophylaxis. It is important to consider the use and timing of medications with neuraxial blockade. When an epidural is used for anesthesia, it is most appropriate to wait until the catheter is removed before starting pharmacologic prophylaxis. See Annotation #9, "Neuraxial Blockade" for more information.

4. VTE Prophylaxis Plan

Patients with contraindications to pharmacologic prophylaxis should receive VTE prophylaxis to the extent possible in relation to procedure-related and patient-related risks.

Patients at high risk for thrombosis and contraindications for pharmacologic prophylaxis present special challenges, and consultation with an anticoagulation expert may be considered.

Patients at risk for developing a VTE should receive patient education, early ambulation, and elastic graded compression stockings. If confined to bed, IPC should be considered. Although no specific studies exist to document the value of patient education and early ambulation to reduce VTE risk, the work group believes these measures are important for patients at risk for VTE, including those in the high-risk group.

Patient Education

All patients, irrespective of their risk for VTE, should receive patient education about VTE. Patient education should include VTE risk, signs and symptoms of VTE, and treatment/prophylactic measures available. Patient education should encourage early and frequent ambulation and flexion/extension exercises for the ankles.

Ambulation

Early mobilization is a therapy to enhance a patient's well-being. This therapy may result in shorter hospitalization due to a specific mobilization program utilized to help patients start regaining their strength. This practice may start mobilization earlier than normally practiced.

Physical therapy may need to be involved as soon as possible, and mobilization will start by sitting and progress to walking if applicable. This should be done every shift or more based on how the patient tolerates mobilization.

Elastic Graded Compression Stockings and Intermittent Pneumatic Compression Devices

In moderate-risk patients with contraindications to pharmacologic prophylaxis, elastic graded compression stockings and intermittent pneumatic compression may be considered an alternative to UFH and LMWH, bearing in mind that there is less data to support this strategy, that hemorrhagic complications are low with

both strategies, and that compliance may be a significant problem when relying on intermittent pneumatic compression alone for VTE prophylaxis.

Several studies have documented the efficacy of elastic graded compression stockings in moderate-VTE-risk patients. Although not studied as a sole method of prophylaxis in high-VTE-risk patients, the work group recommends elastic stocking use in this group as an adjunct to other methods. Mechanical methods include elastic stockings (ES) and intermittent pneumatic compression (IPC), and more recently, foot pumps (FP). All three appear to augment venous return and induce the fibrinolytic system (*Comerota, 1997; Flam, 1996; Tarnay, 1980).* Less often commented upon is the fact that different devices vary in their augmentation of venous blood flow *(Whitelaw, 2001).*

- **Above the knee vs. below-the-knee stockings**

  Numerous literature reports strongly suggest that below-the-knee graduated compression stockings are equally effective to thigh-length stockings in DVT prophylaxis; are easier to use, which improves patient compliance; have fewer associated risks and problems, and are more cost effective *(Byrne, 2001; Ingram, 2003, Porteous, 1989, Benko, 2001, Agu, 1999, Hameed, 2002).*

  Correct fitting of knee-length stockings is important to avoid associated complications such as tourniquet effect.

- **Intermittent pneumatic compression devices**

  Several studies support the use of intermittent pneumatic compression devices as effective in reducing VTE risk in the high-VTE-risk group *(Caprini, 1983; Nicolaides, 1980; Nicolaides, 1983; Scurr, 1987).* Small studies in general surgery patients have shown that IPC devices are effective in reducing the incidence of DVT and by implication, PE (pulmonary embolism) if DVT is considered a marker for PE *(Butson, 1981; Hills, 1972).*

  The effectiveness of IPC is enhanced when combined with elastic graded compression stockings *(Scurr, 1987).* Three other small, randomized studies have shown that IPC is equivalent to UFH in preventing DVT in general surgery patients *(Moser, 1981; Muhe, 1984; Nicolaides, 1983).* Several small, randomized trials in urologic and gynecologic patients have also shown similar outcomes *(Clarke-Pearson, 1993; Coe, 1978; Maxwell, 2001).*

  While complications with IPC are rare, they can occur. Case reports include perineal neuropathy and compartment syndrome, with lithotomy position and weight loss as risk factors *(Lachmann, 1992).*

  Compliance may also be significantly more difficult than with heparin regimens and lead to failure *(Comerota, 1992).* Risk factors for failure of IPC prophylaxis include diagnosis of cancer, history of DVT, and age greater than 60 years *(Clarke-Pearson, 2003).*

  Intermittent pneumatic compression is often not well tolerated by the patient and should be reserved for medical patients who are confined to bed and unable to ambulate or who have contraindications for pharmacologic prophylaxis.

Supporting evidence is of classes: A, C, D, M, R

5. Initiate VTE Prophylaxis Based on Risk Level

All patients irrespective of their risk for VTE should receive patient education about VTE. Patient education should include VTE risk, signs and symptoms of VTE, and available treatment/prophylactic measures available. Patient education should encourage early and frequent ambulation and flexion/extension exercises for the ankles.

Although no specific studies exist to document the value of patient education and early ambulation to reduce VTE risk, the work group believes these measures are important for patients, including those in the high-risk group.

Additional patient-related risk factors may place younger patients and/or those with more minor procedures into a higher-risk category. (See Annotation #2, "Assess VTE Risk for Procedure-Related and/or Patient-Related Risk Factors" for more information) *(Grady, 2000; Hansson, 1999; Rosendaal, 1999)*.

Clinicians should reevaluate the patient and the continuing risk for VTE when there is a change in level of care, change in providers, and prior to discharge. Risk of developing VTE may extend beyond hospitalization. Consideration should be given to extending the period of anticoagulation prophylaxis beyond hospitalization, depending on the patient's risk of VTE and the clinician's judgment.

Supporting evidence is of classes: A, B, R

6. Low VTE Risk

Low-risk patients include those under the age of 40 with no additional risk factors undergoing minor procedures. See Annotation #2, "Assess VTE Risk for Procedure-Related and/or Patient-Related Risk Factors."

In this group, the incidence of proximal DVT is 0.4% and of fatal PE 0.002%. A large review from Denmark studied admissions for VTE in 2,281 patients undergoing outpatient heriorraphy (mean age 47). Only one patient developed a fatal PE *(Riber, 1996)*.

VTE Prophylaxis Plan for Low Risk

No specific measures are required beyond patient education and early ambulation *(Geerts, 2004; Nicolaides, 2006)*.

Supporting evidence is of classes: D, R

7. Moderate/High VTE Risk

Key Points:

- Pharmacologic prophylactic regimens are started one to two hours prior to surgery.
- Aspirin is not recommended as an anticoagulation regimen.
- For short-term prophylactic anticoagulation there are relatively few conditions with excessive bleeding risk or other considerations that would contraindicate anticoagulation.

Moderate-risk patients include:

- major surgery in those less than 40 years of age,
- minor surgery in those age 40-60, and
- minor surgery in those less than age 40 with additional risk factors (prior VTE, cancer, hypercoagulability).

Without prophylaxis, moderate-risk VTE patients have a 2%-4% proximal DVT risk, 1%-2% clinical PE risk, and a 0.1%-0.4% risk of fatal PE *(Geerts, 2004)*.

High-risk patients include:

- minor surgery in those over 60 years of age without additional risk factors,
- major surgery in those over 40 years of age without additional risk factors, and
- minor surgery in those over 40 years of age with additional risk factors (prior VTE, cancer, hypercoagulability).

Without prophylaxis, high-risk VTE patients have a 4%-8% proximal DVT risk, 2%-4% clinical PE risk, and a 0.4%-1.0% risk of fatal PE *(Geerts, 2004)*.

See Annotation #2, "Assess VTE Risk for Procedure-Related and/or Patient-Related Risk Factors."

(Brandjes, 1990; Caprini, 1991; Flordal, 1996; Geerts, 2004; Nicolaides, 2006)

Supporting evidence is of classes: B, D, R

VTE Prophylaxis Plan for Moderate/High VTE Risk

In addition to patient education and early ambulation, all patients with moderate risk for VTE should receive elastic graded compression stockings, intermittent pneumatic compression if immobilized, and pharmacologic prophylaxis unless contraindicated. Pharmacologic regimens reduce compliance issues and have been shown to reduce the incidence of postoperative VTE.

- **Pharmacologic prophylaxis**

  For short-term prophylactic anticoagulation there are relatively few conditions with excessive bleeding risk or other considerations that would contraindicate anticoagulation. Acceptable pharmacologic regimens include UFH and LMWH. Aspirin is not recommended.

  Based on 23 trials of unfractionated heparin, dalteparin, enoxaparin, nadroparin and fondaparinux, there is a reduction of VTE, an increase of bleeding and an uncertain effect on mortality in patients admitted for a medical, non-surgical condition *(Mismetti, 2001; Leizorovicz, 2004)*. See Appendix B, "Summary of VTE Prophylaxis Trials." A recent meta-analysis of hospitalized medical patients showed a significant reduction in PE, a nonsignificant reduction in symptomatic deep vein thrombosis, and a nonsignificant increase in major bleeding. Anticoagulation prophylaxis had no effect in all-cause mortality *(Dentali, 2007)*.

Selecting a Pharmacologic Agent

Three issues that need to be addressed are choice of agent, dosing and duration of therapy. For moderate-risk patients who do not have a contraindication to pharmacologic prophylaxis, the current choice is between LMWH and UFH started 1-2 hours prior to surgery subcutaneous every 8-12 hours. Aspirin has not been shown to be an effective agent in general surgical patients and is not recommended *(Clagett, 1998)*.

UFH is cost effective and effective in reducing the risk of post-operative VTE in moderate-risk patients. While LMWH has the convenience of single-day dosing, it is not superior to UFH and is significantly more expensive. Further, overall complication rates appear similar between UFH and LMWH *(Etchells, 1999; Wille-Jorgensen, 2003)*.

Studies, primarily in patients over 40 years of age, have shown that unfractionated heparin (UFH) is as effective as low-molecular-weight heparin (LMWH) as an anticoagulant prophylactic agent for moderate- and high-risk surgical patients. *[Conclusion Grade I: See Conclusion Grading Worksheet A – Annotations #7, 8 (Selecting Heparin)]*

Several studies have compared LMWH with UFH. A meta-analysis concluded that LMWH doses of less than 3,400 anti-Xa units every day was as effective as UFH. At higher doses, LMWH was slightly superior in preventing VTE but had an increased risk of hemorrhage (including major hemorrhage) *(Mismetti, 2001)*. The European Multicenter Trial concluded that 1,750 anti-Xa units of LMWH (reviparin) was equivalent to 10,000 units UFH, with a slightly decreased rate of bleeding (8.3% vs. 11.8%) *(Kakkar, 1997)*.

The Canadian Colorectal DVT Prophylaxis Trial demonstrated that both heparin 5,000 units every 8 hours and enoxaparin 40 mg every day were equally effective. The minor and major bleeding rate was slightly higher in the LMWH group *(McLeod, 2001)*. The ENOXACAN study group concluded that enoxaparin 40 mg daily and UFH 5,000 units every 8 hours were equally effective, with no significant differences in bleeding complications *(ENOXACAN Study Group, 1997)*. Similar results have been obtained in other studies. While these studies showed a reduction in severe bleeding complications with LMWH (0.6% vs. 1.8% and 1.0% vs. 1.9%, respectively), this did not reach statistical significance in either study *(Kakkar, 1993; Nurmohamed, 1995)*.

General surgical regimens have traditionally been begun preoperatively to increase efficacy. A recent study of LMWH did not show an increased risk of bleeding complications when compared to postoperative administration *(Bjerkeset, 1997)*.

Traditionally, heparin regimens in general surgery have been continued while the patient is hospitalized.

One study compared short (6-10 days) versus prolonged (31 days) enoxaparin administration in patients undergoing abdominal operations for cancer (a high-risk group) and showed a decreased incidence of VTE with prolonged treatment (12% vs. 4.8% p=0.002) *(Bergqvist, 2002)*. On the other hand, a trial from Denmark showed no significant benefit in prolonged prophylaxis *(Lausen, 1998)*. A cost-effectiveness analysis concluded that the marginal cost of prolonged prophylaxis was too high to warrant routine use *(Sarasin, 1996)*.

The ARTEMIS trial showed fondaparinux effective for non-surgical prophylaxis without increasing the risk of clinically relevant bleeding *(Cohen, 2006)*.

See Appendix C, "Pharmacologic Prophylaxis Table" for more information.

- **Mechanical prophylaxis**

  A meta-analysis of eleven studies in moderate-risk patients has shown that graded compression stockings alone results in a 68% risk reduction for DVT *(Wells, 1994)*.

  A more recent meta-analysis by the Cochrane Collaboration of nine randomized controlled trials showed a reduction in the incidence of DVT from 27% in untreated controls to 13% in the treatment group *(Amaragiri, 2003)*. Additional data suggest that below-knee and above-knee stockings are equally effective, and the effectiveness of stockings is enhanced when combined with other measures *(Agu, 1999; Wille-Jorgensen, 1985)*. Side effects are rare, although a proper fit, particularly in the obese, may be difficult in 10%-15% of patients. In general, the data would not support the use of elastic stockings as the sole measure in this group.

  The clinical implications of this are unknown, although augmentation with foot pumps was less than with IPC devices. Foot pumps may be better tolerated and can be applied in cases in which the leg is not appropriate for placement of an IPC device, but the work group is not aware of any studies comparing IPC and foot pumps in general surgery or trauma patients. One study comparing foot pumps to LMWH in total hip patients showed a higher but not statistically significant incidence of DVT in the foot pump arm.

See Annotation #4 for more information on elastic graded compression stockings and intermittent pneumatic compression devices.

Although the work group recommends all of the above non-pharmacologic methods for high-VTE-risk patients, the work group also strongly recommends pharmacologic prophylaxis in these patients unless specifically contraindicated. There is no substitute for critical assessment and judgment on the part of the clinician when considering the relative benefits and risks of prophylactic anticoagulation.

Supporting evidence is of classes: A, C, M, R

8. Very High VTE Risk

Key Points:

- For short-term prophylactic anticoagulation there are relatively few conditions with excessive bleeding risk or other considerations that would contraindicate anticoagulation.
- Consideration should be given to extending the period of pharmacologic prophylaxis beyond hospitalization.
- Aspirin and antiplatelet drugs are not recommended for VTE prophylaxis in other surgical patients or medically ill patients.

Very-high-risk patients include:

- major surgery in patients over 40 years of age with a history of prior VTE or cancer,
- all hip and knee arthroplasty patients,
- all hip fracture patients,
- all major trauma patients, and
- all spinal cord injury patients.

(Rosendaal, 1999)

Without prophylaxis, very-high-risk patients have VTE rates ranging from 40% to 80%. The risk of PE ranges from 4% to 10%, with 0.2% to 5% of patients having a fatal PE *(Ansari, 1997; Geerts, 1994; Khaw, 1993; Stulberg, 1984; Waring, 1991; Warwick, 1995; White, 1998).*

Supporting evidence is of classes: A, B, C, D, R

Prophylaxis Plan for Very High VTE Risk

All patients at very high risk for VTE should receive patient education, early ambulation, elastic graded compression stockings, intermittent pneumatic compression if immobilized, and pharmacologic prophylaxis unless contraindicated. For short-term prophylactic anticoagulation, there are relatively few conditions with excessive bleeding risk or other considerations that would contraindicate anticoagulation. Aspirin is not recommended for VTE prophylaxis in other surgical patients or medically ill patients.

- **Pharmacologic prophylaxis**

  Acceptable anticoagulation regimens include LMWH, fondaparinux and adjusted dose warfarin to keep the INR between 2.0 and 3.0. UFH is not recommended.

  Consideration should be given to extending the period of anticoagulation prophylaxis beyond hospitalization, depending on the length of hospital stay. If anticoagulation is contraindicated, placement of an IVC filter should be considered in this patient group.

Based on 23 trials of unfractionated heparin, dalteparin, enoxaparin, nadroparin and fondaparinux, there is a reduction of VTE, an increase of bleeding and an uncertain effect on mortality in medically ill patients *(Mismetti, 2001; Leizorovicz, 2004)*. See Appendix B, "Summary of VTE Prophylaxis Trials." A recent meta-analysis of hospitalized medical patients showed a significant reduction in PE, a nonsignificant reduction in symptomatic deep vein thrombosis, and a nonsignificant increase in major bleeding. Anticoagulation prophylaxis had no effect in all-cause mortality *(Dentali, 2007)*.

The ARTEMIS trial showed fondaparinux effective for non-surgical prophylaxis without increasing the risk of clinically relevant bleeding *(Cohen, 2006)*.

See Appendix C, "Pharmacologic Prophylaxis Table" for more information.

- **Ambulation and mechanical prophylaxis**

  Although no specific studies exist to document the value of patient education and early ambulation to reduce VTE risk, the work group believes these measures are important for all VTE risk patients, including those in the very-high-risk group. Several studies have documented the efficacy of elastic stockings in moderate- and high-VTE-risk patients (See Annotation #4, "VTE Prophylaxis Plan").

  Although not studied as a sole method of prophylaxis in very-high-VTE-risk patients, the work group recommends elastic stocking use in this group as an adjunct to other methods. Several studies support the use of pneumatic compression devices as effective in reducing the VTE rate in the very-high-VTE-risk group *(Fordyce, 1992; Hartman, 1982; Stranks, 1992; Warwick, 1998; Wilson, 1992)*.

Although the work group recommends all of the above non-pharmacologic methods for very-high-VTE-risk patients, the work group also strongly recommends prophylactic anticoagulation in these patients unless contraindicated.

(Ansari, 1997; Geerts, 1994; Khaw, 1993; Stulberg, 1984; Waring, 1991; Warwick, 1995; White, 1998)

Supporting evidence is of classes: A, B, C, D, M, R

Use of Aspirin Following Hip/Knee Arthroplasty

Although it remains controversial, interest persists in the orthopedic community regarding the use of aspirin for VTE prophylaxis following elective hip and knee arthroplasty. The debate over the use of aspirin for VTE prophylaxis is occurring in Minnesota and across the U.S. The work group has put in a pro/con forum to illustrate this debate. The ACCP recommends against the use of aspirin. Aspirin is not recommended for routine VTE prophylaxis following hip/knee arthroplasty but may be considered in some circumstances. Further study is needed.

- **Con:**

  The ACCP recommendations against aspirin are based on the failure of aspirin to demonstrate a similar reduction in the rate of venographically proven DVT compared to other anticoagulants *(Geerts, 2004)*. The endpoints of a venographically proven DVT has long been the diagnostic standard in thromboprophylaxis trials because of the sensitivity of detecting DVT and the availability of images for blinded study adjudication for most of the studies that compared aspirin, LMWH, UFH and other anticoagulants.

  There is some evidence that aspirin may provide some protection against VTE; however, that is based on methodologically limited studies *(Geerts, 2004)*. Additionally, while there may be disagreement between the endpoint of a venographically proven DVT and a symptomatic DVT/PE as an endpoint, aspirin was not shown to be significantly beneficial compared to other anticoagulation agents *(Westrich, 1996)*.

Fatal PE and non-fatal PE/DVT are not the only concern when evaluating VTE prophylaxis therapy. It is important to acknowledge that VTE is also the source of significant, long-term morbidity from its non-fatal sequelae, and it is important to reduce all VTE events, even non-fatal events, because of the impact on the quality of life for patients *(Prandoni, 1996)*. Other anticoagulation agents reduce the rate of DVT significantly more than aspirin *(Gent, 1996)*. A recent meta-analysis published in Lancet did show a reduction of risk for PE and DVT by one third; however, what the study was not designed to show was whether aspirin is as effective as other anticoagulation agents in preventing post-discharge VTE *(Pulmonary Embolism Prevention (PEP) Trial Collaborative Group, 2000)*. Randomized controlled studies comparing aspirin to anticoagulant prophylaxis or placebo are needed to help determine aspirins true efficacy.

Lastly, it is true that surgical procedures change rapidly and it is unknown what the overall burden of disease for DVT is with these new approaches to surgery, anesthesia and postoperative rehabilitation. Further randomized controlled studies to help determine the incidence of VTE associated with these less invasive techniques are needed before final recommendations can be made.

- **Pro:**

  The ACCP recommendations against aspirin are based on the failure of aspirin to demonstrate a similar reduction in the rate of venographically proven DVT compared to other anticoagulants.

  However, the value of this particular measure (a positive venogram) has been questioned. Several studies have shown comparable and low rates for aspirin utilizing other potential measures, including symptomatic DVT, symptomatic non-fatal PE, fatal PE and mortality. Sarmiento in 1999 reported on 1492 total hip arthroplasties where aspirin was the only post-operative anticoagulant utilized. The rate of fatal PE was 0.13%, symptomatic non-fatal PE 0.94%, and symptomatic DVT 1.01% *(Sarmiento, 1999)*. He followed this up in 2005, reporting 1835 total hip arthroplasties where again the only post-operative anticoagulant was aspirin. The rate of fatal PE was 0.10%, symptomatic non-fatal PE 0.9%, and symptomatic DVT 0.9% *(Sarmiento, 2004)*. Freedman in 2000 reported a meta-analysis of 10,929 total hip arthoplasties treated with a variety of anticoagulants post-operatively, including aspirin, low-molecular-weight heparin, and warfarin. There were no significant differences among agents with regard to the risk of fatal pulmonary embolism or mortality from any cause *(Freedman, 2000)*.

  Similar data exists for total knee arthroplasty. Westrich in 2000 reported a meta-analysis of 6,001 total knee arthroplasties treated with a variety of anticoagulants post-operatively, including aspirin, low-molecular-weight heparin, and warfarin. No significant difference was seen between agents with regard to the rate of symptomatic PE *(Westrich, 2000)*. Brookenthal in 2001 reported a meta-analysis of 3,482 total knee arthroplasties treated with a variety of anticoagulants post-operatively, including aspirin, low-molecular-weight heparin, and warfarin. No significant difference was found with regard to the rate of symptomatic non-fatal PE, fatal PE or mortality from any cause *(Brookenthal, 2001)*. Lotke in 2006 reported a series of 3,402 total knee arthroplasties treated with aspirin as the only post-operative anticoagulant. The rate of fatal PE was 0.06% to 0.14% *(Lotke, 2006)*.

  Westrich reported a randomized series of 275 total knee patients comparing aspirin with enoxaparin. All patients were evaluated with ultrasound. There was no difference in the rate of ultrasound-proven DVT between the two groups *(Westrich, 2006)*.

  One can conclude that although studies have demonstrated that aspirin has not been as effective as other anticoagulants at reducing the rate of venographically proven DVT, there is no apparent difference between aspirin and other anticoagulants with regard to the rate of symptomatic non-fatal PE, fatal PE, or mortality from any cause. Furthermore, there have been no studies demonstrating an improvement in overall outcome with LMWH, fondaparinux or warfarin compared to aspirin. In

fact, the increased risk of bleeding associated with these agents may create different complications that may compromise the overall outcome more than a positive venogram.

Finally, the entire process of total hip and knee arthroplasty is changing rapidly. The goal has been to mobilize these patients as rapidly as possible following surgery by utilizing a multimodal approach. This approach includes an increasing emphasis on pre-operative education for patients, a trend to regional anesthesia, new less invasive surgical techniques, decreasing reliance on narcotic medications post-operatively, and increasingly aggressive rehabilitation protocols. Patients are now frequently out of bed and ambulating the day of surgery. All the studies upon which the recommendation against aspirin are based were completed at a time when things were much different than today. The best study would consist of a randomized prospective comparison of anticoagulants with a modern surgical experience utilizing overall outcome as the measure.

Unfortunately, such a study does not exist. We are left to rely on our medical instincts when it comes to making a decision that will affect our patients' overall outcome following elective hip and knee arthroplasty.

Supporting evidence is of classes: A, B, D, M, R

9. Neuraxial Blockade

Neuraxial blockade is not a contraindication for pharmacologic prophylaxis. It is important to consider the use and timing of medications with neuraxial blockade. When an epidural is used for anesthesia, it is most appropriate to wait until the catheter is removed before starting pharmacologic prophylaxis. Neuraxial blockade should generally be avoided in patients with a clinical bleeding disorder.

General guidelines:

1. 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, numbness, incontenience) after injections, during infusions and after discontinuation of infusions.
2. Both insertion and removal of neuraxial catheters are significant events. The timing of those events and the timing of any anticoagulation drugs should be taken into consideration, as well as the pharmacokinetics and pharacodynamics of the specific anticoagulant drugs.
3. The emergence of new drugs and unexpected clinical scenarios can render any guideline obsolete. Consultation with an anesthesiologist experienced in regional anesthesia is essential for novel situations.
4. 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 anticoagulation and can be used for detailed management. These guidelines are available at http://www.asra.com.

(Horlocker, 2003)

Neuraxial blockade (spinal or epidural anesthesia) is a valuable tool for both anesthesiologists and surgeons. The Cochrane Reviews and other sources have listed the usefulness of neuraxial blockade for both intraoperative anesthesia as well as postoperative analgesia. There are groups of patients that demonstrate improved morbidity and mortality with the use of regional rather than general anesthesia. Similarly the usefulness of VTE prophylaxis in preventing morbidity and mortality in surgical patients has been well established. However, there is concern about an increased risk of perispinal hematoma in patients receiving antithrombotic medications for VTE prophylaxis in the setting of neuraxial blockade.

Perispinal hematoma is a rare but serious complication of neuraxial blockade. Thus, it is important to consider both the use and the timing of antithrombotic medications in these patients.

(Geerts, 2004; Millar, 1996; Tyagi, 2002)

Supporting evidence is of classes: D, R

Heparin with Neuraxial Blockade

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

- **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 or she should be assessed for heparin-induced thrombocytopenia (HIT) *(Horlocker, 1995)*. Optimally, the insertion of an epidural catheter occurs after three to four half-lives of the drug has elapsed. Depending on the drug and the renal clearance of the patient, this can be 12-24 hours for UFH or LMWH. An epidural catheter should be removed when the anticoagulation effect is at its minimum, approximately two hours before the next scheduled injection. Anticoagulation therapy may be resumed two hours after the catheter has been removed.

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

Supporting evidence is of classes: B, R, Not Assignable

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 in the study below *(Horlocker, 1994)*.

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

Supporting evidence is of classes: B, D

Newer Anticoagulant Drugs with Neuraxial Blockade

The use of the newer Factor Xa inhibitor, fondaparinux or the thrombin inhibitors related to hirundin is a relative contraindication to all regional anesthesia. The emergence of other newer anticoagulant drugs requires that each be evaluated with regard to its safety in combination with regional anesthesia.

In all such circumstances, consultation with an anesthesiologist experienced in regional anesthesia is recommended.

Appendix A – Heart Failure Classification

New York Heart Association Classification

The New York Heart Association (NYHA) classification is a four-level scheme for grading the functional incapacity of patients with cardiac disease. NYHA levels can be described as follows:

Level/Class	Description	Simple Description
I	Cardiac disease without resulting limitations of physical activity	Asymptomatic
II	Slight limitation of physical activity – comfortable at rest, but ordinary physical activity results in fatigue, dyspnea or anginal pain	Symptomatic with moderate exertion
III	Marked limitation in physical activity – comfortable at rest, but less than ordinary physical activity causes fatigue, dyspnea or anginal pain	Symptomatic with minimal exertion
IV	Inability to carry on any physical activity without discomfort or symptoms at rest	Symptomatic at rest

Heart Failure Classification Comparison

NYHA Functional Classification Compared to ACC/AHA 2001 Staging

	ACC/AHA, 2001		NYHA
A	At high risk of developing HF, but without structural heart disease or symptoms of HF	None	
B	Structural heart disease, but without symptoms of HF	I	Asymptomatic
C	Structural heart disease with prior or current symptoms of HF	II	Symptomatic with moderate exertion
		III	Symptomatic with minimal exertion
		IV	Symptomatic at rest
D	Refractory end-stage HF requiring specialized interventions	IV	

ACC = American College of Cardiology, AHA = American Heart Association,
NYHA = New York Heart Association, HF = Heart Failure

The ACC/AHA heart failure grading scheme takes into consideration the natural history, and progressive nature of heart failure has been recommended in the most recent ACC/AHA guidelines.

For each of these classes, recommendations for prevention, ongoing surveillance for disease progression, and specific medical therapy is outlined. This new classification scheme is in the stages of early adoption presently and is used conjunction with the NYHA classification described above.

Appendix B – Summary of VTE Prophylaxis Trials

Trials of UFH vs. Control

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**UFH**	**Control**	**UFH**	**Control**	**UFH**	**Control**	**UFH**	**Control**
Gallus, 1973	1/38	9/40						
Beich, 1981	2/50	13/50	0/50	2/50	NE	NE	0/50	0/50
Cade, 1982	15/154	15/80	NE	NE	NE	NE	0/154	0/80
Halkin, 1982					53/679	74/769		
Ibarra-Perez, 1988	1/33	12/46	0/39	3/46	NE	NE	4/39	0/46
Gardlung, 1996	NE	NE	34/5776	74/5917	304/5776	333/5917	14/5776	6/5917
TOTAL	19/275 6.9%	49/216 22.7%	34/5865 0.6%	79/6013 1.3%	357/6455 5.5%	407/6686 6.1%	18/6019 0.3%	6/6093 0.1%

Trials of Dalteparin vs. Control

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**Dalteparin**	**Control**	**Dalteparin**	**Control**	**Dalteparin**	**Control**	**Dalteparin**	**Control**
Leizorovicz, 2004	33/1759	64/1739	5/1759	4/1739	43/1829	42/1807	9/1829	3/1807

Trials of Enoxaparin vs. Control

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**Enoxaparin**	**Control**	**Enoxaparin**	**Control**	**Enoxaparin**	**Control**	**Enoxaparin**	**Control**
Dahan, 1986	4/132	12/131	0/135	3/135	1/135	6/135	1/135	3/135
Samama, 1999	16/367	40/371	0/367	3/371	41/367	50/371	12/367	7/371
TOTAL	20/499 4.0%	52/502 10.4%	0/502 0.0%	6/506 1.2%	42/502 8.4%	56/506 11.1%	13/502 2.6%	10/506 2.0%

Trials of Nadroparin* vs. Control

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**Nadroparin**	**Control**	**Nadroparin**	**Control**	**Nadroparin**	**Control**	**Nadroparin**	**Control**
Bergmann, 1996	NE	NE	10/1230	17/1244	124/1230	128/1244	NE	NE
Fraisse, 2000	13/84	24/85	0/108	0/113	18/108	17/113	6/108	3/113
TOTAL	13/84 15.5%	24/85 28.2%	10/1338 0.7%	17/1357 1.3%	142/1338 10.6%	145/1357 10.7%	6/108 5.6%	3/113 2.7%

Trials of Dalteparin vs. UFH

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**Dalteparin**	**UFH**	**Dalteparin**	**UFH**	**Dalteparin**	**UFH**	**Dalteparin**	**UFH**
Poniewierski, 1988	NE	NE	0/100	0/100	1/100	0/100	NE	NE
Harenberg, 1990	3/84	4/82	NE	NE	3/84	1/82	0/84	1/82
TOTAL	3/84 3.6%	4/82 4.9%	0/100 0.0%	0/100 0.0%	4/184 2.2%	1/182 0.5%	0/84 0.0%	1/82 1.2%

Trials of Enoxaparin vs. UFH

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**Enoxaparin**	**UFH**	**Enoxaparin**	**UFH**	**Enoxaparin**	**UFH**	**Enoxaparin**	**UFH**
Bergmann, 1996 (ESMG)	9/207	10/216	1/216	0/223	7/216	8/223	1/216	2/223
Lechler, 1996	1/477	4/482	0/477	4/482	7/477	11/482	2/477	9/482
Kleber, 1998	19/239	22/212	1/239	1/212	28/332	30/333	1/332	1/333
Harenberg, 1999	21/106	37/106						
TOTAL	50/1029 4.9%	73/1016 7.2%	2/932 0.2%	5/917 0.5%	42/1025 4.1%	49/1038 4.7%	4/1025 0.4%	12/1038 1.2%

Trials of Nadroparin* vs. UFH

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**Nadroparin**	**UFH**	**Nadroparin**	**UFH**	**Nadroparin**	**UFH**	**Nadroparin**	**UFH**
Aquino, 1990	1/49	1/50	0/49	0/50	1/49	2/50	0/49	0/50
Manciet, 1990	0/129	1/127	NE	NE	8/129	8/127	1/129	4/127
Forcette, 1995	3/146	3/149	0/146	1/149	6/146	7/149	0/146	4/149
Harenberg, 1996	6/726	4/710	5/810	6/780	23/810	9/780	5/810	4/780
TOTAL	10/1050 1.0%	9/1036 0.9%	5/1005 0.5%	7/979 0.7%	38/1134 3.4%	26/1106 2.4%	6/1134 0.5%	14/1106 1.3%

Trials of LMWHs vs. UFH

	Deep Vein Thrombosis		Pulmonary Embolism		Death		Major Bleeding	
Study	**LMWH**	**UFH**	**LMWH**	**UFH**	**LMWH**	**UFH**	**LMWH**	**UFH**
Dalteparin	3/84	4/82	0/100	0/100	4/184	1/182	0/84	1/82
Enoxaparin	50/1029	73/1016	2/932	5/917	42/1025	49/1038	4/1025	12/1038
Nadroparin	10/1050	9/1036	5/1005	7/979	38/1134	26/1106	6/1134	14/1106
TOTAL	63/2163 2.9%	86/2134 4.0%	7/2037 0.3%	12/1996 0.6%	84/2343 3.6%	76/2326 3.3%	10/2243 0.4%	27/2226 1.2%

*Nadroparin is no longer available in the U.S.

Based on 23 trials of unfractionated heparin, dalteparin, enoxaparin, nadroparin and fondaparinux, there is a reduction of VTE, an increase of bleeding and an uncertain effect on mortality.

Until such statically unequivocal trials are available, it is the recommendation of this group, based on the above-mentioned 23 trials, that patients admitted to the hospital for medical reasons should be considered for pharmacologic VTE prophylaxis if they have a high risk for VTE and do not have a contraindication to antithrombotics. Patients with renal insufficiency (measured or calculated creatinine clearance less than 30) who are eligible for pharmacologic VTE should receive unfractionated heparin.

Though we are not aware of any trials of mechanical prophylaxis (early ambulation, elastic support stockings, intermittent pneumatic compression), it is the recommendation of this group that all patients admitted to the hospital for medical reasons ambulate as early and as often as possible. Elastic support stockings may also be considered. Intermittent pneumatic compression is often annoying to the patient and should be reserved for medical patients who have a high risk of VTE, have a contraindication to antithrombotics and are confined to bed.

Appendix C – Pharmacologic Prophylaxis Table

	Dalteparin	Enoxaparin	Fondaparinux	UFH	Warfarin	Duration of Prophylaxis
Orthopedic Hip Replacement	2,500 units 2-8 hr. before surgery then 5,000 units every 24 hr. post-op or 5,000 units 10-14 hr. before surgery then every 24 hr. post-op	30 mg every 12 hr. beginning 12 hr. post-op or 40 mg every 24 hr. beginning 9-15 before surgery	2.5 mg every 24 hr. beginning 6-8 hr. post-op	Not Recommended	INR 2.5 (2.0 – 3.0) beginning day of surgery	Minimum 10 days post-op Consider extending prophylaxis to 28-35 days post-op
Hip Fracture	5,000 units/daily beginning 12-24 hr. post-op If surgery is delayed, initiate between admission and surgery	30 mg twice daily beginning 12 hr. post-op If surgery is delayed, initiate between admission and surgery	2.5 mg/daily beginning 6-8 hr. post-op If surgery is delayed, initiate between admission and surgery	Not Recommended	INR 2.5 (2.0 – 3.0) beginning day of surgery	Minimum 10 days post-op Consider extending prophylaxis to 28-35 days post-op
Knee Replacement	2,500 units 2-8 hr. before surgery then 5,000 units every 24 hr. post-op or 5,000 units 10-14 hr. before surgery then every 24 hr. post-op	30 mg every 12 hr. beginning 12 hr. post-op	2.5 mg every 24 hr. beginning 6-8 hr. post-op	Not Recommended	INR 2.5 (2.0 – 3.0) beginning day of surgery	Minimum 10 days post-op
Multiple Trauma	5,000 units every 24 hr. beginning 12-24 hr. post-op	30 mg every 12 hr. beginning 12 hr. post-op				Until discharge unless there is impaired mobility
Spinal Cord Injury	5,000 units every 24 hr. beginning 12-24 hr. post-op	30 mg every 12 hr. beginning 12 hr. post-op				

Appendix C – Pharmacologic Prophylaxis Table

	Dalteparin	Enoxaparin	Fondaparinux	UFH	Warfarin	Duration of Prophylaxis
Elective Spine Surgery	5,000 units every 24 hr. post-op	40 mg every 24 hr. post-op		5,000 units every 8-12 hr. post-op		
Neurosurgery	5,000 units every 24 hr. post-op	40 mg every 24 hr. post-op		5,000 units every 8-12 hr. post-op		
Oncology Surgery *(Patients with active cancer are at the very highest risk for thrombolic events)*	5,000 units every 24 hr. beginning the evening prior to surgery	30 mg every 12 hr	2.5 mg every 24 hr. post-op	5,000 units every 8-12 hr		Continue 2-4 weeks after discharge
General Surgery Low Risk						
Mod Risk	2,500 units 1-2 hr. before surgery and then every 24 hr	40 mg 2 hr. before surgery and then every 24 hr		5,000 units every 12 hr		Until ambulatory
High Risk	5,000 units 1-2 hr. before surgery and then every 24 hr	40 mg 2 hr. before surgery and then every 24 hr		5,000 units every 8-12 hr		Until discharge
Gynecologic Surgery • Including Caesarean Section	5,000 units 1-2 hr. before surgery and then every 24 hr	40 mg 2 hr. before surgery and then every 24 hr		5,000 units every 12 hr		Until discharge
Urologic Surgery	5,000 units 1-2 hr. before surgery and then every 24 hr	40 mg 2 hr. before surgery and then every 24 hr		5,000 units every 12 hr		
Medical Patients Low and Moderate Risk	5,000 units every 24 hr. beginning at admission	40 mg every 24 hr. beginning at admission	2.5 mg every 24 hr. beginning at admission			Until discharge unless there is impaired mobility
High and Very High Risk • Including ICU	5,000 units every 24 hr. beginning at admission	40 mg every 24 hr. beginning at admission	2.5 mg every 24 hr. beginning at admission	5,000 units every 8-12 hr. beginning at admission		Until discharge unless there is impaired mobility
Renal Insufficiency (CRCL less than 30 mL/min)	Reduce dose per pharmacist recommendation	30 mg every 24 hr	Contraindicated			
Severely Obese Patients (BMI 35 or more)	Increase dose by 25%	Increase dose by 25%				

The information in this table was compiled from the following sources: Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004; 126:338S-400S, Nicolaides AN, Fareed J, Kakkar AK, et al. Prevention and treatment of venous thromboembolism international consensus statement. *Int Angiol* 2006; 25:101-161, and manufacturer recommendations. This information is current as of April 2007. For the most up-to-date medication and prescribing information, consult with your pharmacy or consider the following sources: www.epocrates.com, www.micromedex.com, www.uptodate.com, www.pdr.net.

Document Drafted
Jan – May 2003

First Edition
Nov 2003

Second Edition
Jul 2005

Third Edition
Jul 2006

Fourth Edition
Begins Jul 2007

Released in June 2007 for Fourth Edition.
The next scheduled revision will occur within 12 months.

Availability of references

References cited are available to ICSI participating member groups on request from the ICSI office. Please fill out the reference request sheet included with your guideline and send it to ICSI.

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Brief Description of Evidence Grading

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

A full explanation of these designators is found in the Foreword of the guideline.

II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in the Foreword and are assigned a designator of +, -, or ø to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

The symbols **+**, **–**, **ø**, and **N/A** found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

+ indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

– indicates that these issues have not been adequately addressed;

ø indicates that the report or review is neither exceptionally strong or exceptionally weak;

N/A indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

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Conclusion Grading Worksheet A – Annotations #7, 8 (Selecting Heparin)

Work Group's Conclusion: Studies, primarily in patients over 40 years of age, have shown that unfractionated heparin (UFH) is as effective as low-molecular-weight heparin (LMWH) as an anticoagulant prophylactic agent for moderate- and high-risk surgical patients.

Conclusion Grade: I

Author/Year	Design Type	Class	Quality +,–,**0**	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Kakkar et al., 1993	RCT	A	**0**	-Male and female patients; > 40 yrs old, major elective abdominal surgery; surgeons in 19 hospitals -Excluded: known allergy to heparin, taking oral anticoagulants before admission, severe hemorrhagic episode in past 3 months unrelated to surgery, known bleeding diathesis, scheduled for reoperation during study period, not actively avoiding pregnancy, any other contraindication to heparin -Randomized to 2,500 IU LMWH once daily + placebo saline or 5,000 IU standard heparin (LDUH) twice daily (subcutaneous); began 1-4 hrs before surgery and continued ≥5 days -Follow-up: 4-8 wks after operation -Investigated clinical signs of DVT (venography) and PE (V/Q scan or pulmonary angiography) -Assessed intra- and postoperative bleeding loss	-1,894 received LMWH, 1,915 received LDUH; groups similar at baseline except higher history of chronic respiratory disease in LDUH group and history of oral contraceptive or hormone replacement therapy in past 6 months in LMWH group -37.6% of each group had operations for cancer; mean length of inpatient stay = 6 days (each group) -Perioperative deaths: 3.3% of LMWH group and 2.5% of LDUH group (RR=1.36, 95%CI 0.93-1.97) -Thromboembolic events: 1.0% of LMWH group and 1.1% of LDUH group (RR=0.87, 95%CI 0.47-1.61); PE in 0.7% and DVT in 0.6% of each group -Intraoperative bleeding: excessive in 5.9% of LMWH group (0.5% discontinued tx) and 5.7% of LDUH group (0.5% discontinued tx) -Postoperative bleeding: excessive in 6.5% of LMWH group (1.4% discontinued tx) and 6.8% of LDUH group (1.6% discontinued tx) -Perioperative bleeding rated as major in 3.6% of LMWH group and 4.8% of LDUH group (RR=0.77, 95%CI 0.56-1.04) with more wound hematoma (RR=0.52, 95%CI 0.33-0.83), re-operations because of bleeding (RR=0.55, 95%CI 0.31-0.98), and severe bleeding (RR=0.51, 95%CI 0.29-0.89) in LDUH group; more minor bleeding in LDUH group (7.9% vs. 6.2%, $p<0.05$) due to more injection site bruising (RR=0.62, 95%CI 0.47-0.83) -Patients with excessive perioperative bleeding were older, more likely to be male, to have cancer, or to be taking NSAIDs (all $p<0.05$) -Other complications: no differences between groups -Follow-up period: 0.60% of LMWH group and 0.53% of LDUH group died; 0.9% of LMWH and 0.6% of LDUH group had thromboembolic event	-LMWH and LDUH were of similar efficacy. The frequency of major bleeding was 23% lower with LMWH but the difference was not significant. Secondary endpoints (including wound hematomas and need for re-operation) were observed less frequently in the LMWH group. Both agents seemed to be of similar efficacy in preventing postoperative venous thromboembolism complications. NOTES: major surgery defined as procedure under general anesthesia, >30 min duration, ≥6 days in hospital; did sample size estimation (3,600 patients needed for 90% probability of detecting 30% difference at 0.05 level); added 10% for protocol violations; analysis by intention-to-treat; aspirin or other NSAIDs given concurrently in 7.4% of LMWH group and 8.0% of LDUH group

Author/Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Nurmohamed et al., 1995	RCT	A	0	-Male and female patients; >40 years; major general surgery; 20 centers -Excluded: allergy for heparin, iodine, or contrast material; documented bleeding tendency; pregnancy; use of drugs interfering with coagulation -Randomized to 5,000 LDUH three times/day or 20 mg enoxaparin once/day (+ 2 placebo injections); started 2 hrs postoperatively and continued for 10 days or until discharge; subcutaneous -Daily surveillance for VTE, bleeding, other adverse events -DVT confirmed with venography; PE with V/Q or pulmonary angiography -Blood loss monitored (intra- and postoperative)	-709 patients in LDUH group, 718 in LMWH group; no differences between groups at baseline -Thromboembolic complications suspected: 6.4% of LDUH group, 8.1% of LMWH group (either abnormal fibrinogen uptake test or clinical suspicion); confirmed complications in 3.7% of LDUH group and 6.0% of LMWH group (p=0.054) -Adjustment for cancer, weight, varicose veins, and duration of operation did not affect the treatment comparison -Major bleeding: 2.5% of LDUH group, 1.5% of LMWH group -Reoperation for bleeding: 1.8% of LDUH group, 0.6% of LMWH group (p=0.03) -Minor bleeding: 16.3% of LDUH group, 13.8% of LMWH group -No differences in intra- or postoperative bleeding volumes or number of patients transfused -Deaths: 6 from LDUH group (2 with major bleeding), 4 from LMWH group (1 PE, 1 with major bleeding)	-LMWH appears as effective and as safe as LDUH for prophylaxis of postoperative VTE. In view of its more convenient way of administration, LMWH might be preferred for thromboprophylaxis. NOTES: major surgery defined as >45 minutes with general anesthesia; did sample size estimation (600 patients per group for power of ≥80% to detect reduction of VTE events from 8% of LDUH group to 4% of enoxaparin group at p=0.05) *Work Group's Comments: not all patients with suspected thromboembolic complications underwent objective testing*

Author/Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
ENOXACAN Study Group, 1997	RCT	A	0	-Male and female patients; >40 years; 10 countries/34 investigators; open elective curative surgery for abdominal or pelvic cancer; expected survival ≥6 mo -Excluded: renal or hepatic insufficiency; laparoscopic surgery; hypersensitivity to contrast media, heparin, or LMWH; recent cerebrovascular thrombosis, hemorrhage, neurosurgery, or cerebral metastases; generalized bleeding disorder; endocarditis; active peptic ulcer; untreated arterial hypertension; DVT and/or PE in past 3 months; treatment with heparin, LMWH, or oral anticoagulant in past 5 days; pregnancy/lactation -Randomized to 5,000 units LDUH 3X/day or 40 mg enoxaparin 1X/day + 2 placebo injections/day; started 2 hr before operation, venography on day 10; subcutaneous -DVT confirmed with venography; PE with V/Q and/or pulmonary angiography -Blood loss and bleeding monitored	-560 in LDUH group, 556 in enoxaparin group; evaluable population was 319 in LDUH group and 312 in enoxaparin group; no differences at baseline -Postoperative VTE: 18.2% of LDUH group and 14.7% of LMWH group (OR=0.78, 95%CI 0.51-1.19) -Hemorrhage: 17.1% in LDUH group, 18.7% in LMWH group (major hemorrhage in 2.9% of LDUH group and 4.1% of LMWH group) (not significant) -No differences in adverse events -3 month follow-up: 13 patients lost or information missing; 60 deaths (34 LDUH group, 26 enoxaparin group); 9 of 60 deaths were thromboembolic in origin; 27 LDUH and 25 LMWH patients had further surgery	-Enoxaparin, 40 mg once daily, is as safe and as effective as unfractionated heparin three times daily in preventing venous thromboembolism in patients undergoing major elective surgery for abdominal or pelvic malignancy. NOTES: planned duration of surgery >45 min with hospitalization of ≥6 days; all patients had bilateral venography within 24 hours of last injection (if not before due to symptoms); did sample size estimation (400 patients per group for power of 80% to conclude that enoxaparin was no different from LDUH by more than 6% if true frequency of DVT was 10% in both groups); increased to total of 1,150 to account for missed or inadequate venograms; 5 patients were <40 yrs; surgery reclassified as palliative in 13.4%; some surgeries <45 min *Work Group's Comments: patients who did not undergo venography or with inadequate venography were excluded from analysis*

Author/Year	Design Type	Class	Quality +,–,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
McLeod et al., 2001	RCT	A	0	-Adult patients; part or all of colon or rectum resected; 10 hospitals -Excluded: required anticoagulant, antiinflammatory, or antiplatelet therapy; hepatic or renal failure; history of systemic bleeding diathesis or heparin-induced thrombocytopenia; uncontrolled hypertension; hemorrhage (stroke or GI) in past 3 mos; major psychiatric disorder; systemic allergy to contrast material; pregnant or lactating -Randomized to calcium heparin (LDUH) (5,000 units every 8 hrs) or enoxaparin (LMWH) (40 mg 1X/day plus 2 placebo injections); subcutaneous; began 2 hrs before surgery; 1 other injection that day then 3 per day for up to 10 days -Bilateral ultrasound and venography on or before day 9; suspected DVT evaluated with ultrasound then venography if positive; suspected PE with V/Q then angiography -Blood loss and bleeding monitored	-1,349 randomized (of 2,354 eligible) - 675 to LDUH, 674 to LMWH; groups did not differ at baseline -Final analysis based on 936 (468 per group, no differences between groups); 53 were found to be ineligible; 360 with inadequate venography, withdrawn consent, bleeding, death, and other reasons -Compliance with study drug rated as high -VTE rate: 9.4% in each group; one nonfatal, symptomatic PE (in LMWH group); no deaths attributed to VTE -Subgroups: a) Inflammatory bowel disease: lower VTE rate in LDUH group (2.9% vs. 9.0%, p=0.04) b) Obese patients (BMI>30%): higher VTE rate in LDUH group (26.3% vs. 9.4%, p=0.001) c) Cancer, age >50, history of VTE, undergoing rectal dissection: no differences in VTE rate between groups -Intra- and postoperative blood loss, # units transfused, proportion requiring transfusion, reoperation for bleeding: no differences between groups -Total bleeding event rate: lower in LDUH group (6.2% vs. 10.1%, p=0.003) (excess of minor bleeding events in LMWH group, p=0.03) -Thrombocytopenia: 0.9% of each group	-Both heparin (5,000 units subcutaneously every 8 hours) and enoxaparin (40 mg subcutaneously once daily) provide highly effective and safe prophylaxis for patients undergoing colorectal surgery. However, given the current differences in cost, prophylaxis with low-dose heparin remains the preferred method. NOTES: eligible surgeries performed under general anesthesia and at least 1 hour long; other methods of pharmacological or mechanical prophylaxis were not allowed; use of NSAIDs was not allowed; did sample size estimation (risk of VTE estimated at 12.5% in LDUH group; 470 patients per group needed to detect difference of 5.5% with power of 80% at 0.05 level)

Author/Year	Design Type	Class	Quality +,–,Ø	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ *Work Group's Comments (italicized)*
Mismetti et al., 2001	Meta-analysis	M	Ø	-Randomized trials comparing prophylactic LMWH with any other prophylactic treatment in patients undergoing general surgery; control group; outcome of DVT, PE, major hemorrhage, or death -Includes Kakkar et al., Nurmohamed et al., & ENOXACAN studies (cited above)	-51 studies comparing a LMWH with LDUH (48,624 patients); LMWHs included certoparin (15 studies), dalteparin (13 studies), enoxaparin (8 studies), nadroparin (5 studies), parnaparin (4 studies), and others (1 study each); LDUH doses ranged from 2,500 units 2X/day to 5,000 units 3X/day -Relative risks comparing LMWH with LDUH: a) Asymptomatic DVT: 0.90 (95%CI 0.79-1.02) b) Clinical PE: 0.88 (95%CI 0.64-1.20) c) Clinical thromboembolism: 0.71 (95%CI 0.51-0.99) d) Death: 1.04 (95%CI 0.89-1.20) e) Major hemorrhage: 0.89 (95%CI 0.75-1.05) f) Transfusion: 1.03 (95%CI 0.94-1.12) -With double-blind studies only: no significant differences between LMWH and LDUH -No differences between LMWH and LDUH for cancer or non-cancer surgery	-LMWH seems to be as effective and as safe as LDUH for thromboprophylaxis in general surgery. -NOTES: general surgery defined as abdominothoracic (excluding vascular), urological and gynecological, and surgery for malignant disease; excluded orthopedic, non-cancer thoracic, extra-corporeal thoracic, and non-cancer laparoscopic surgery.
Wille-Jorgensen et al., 2003	Systematic Review	M	–	-Randomized trials comparing LDUH and LMWH in major colorectal surgery patients; objective diagnostic measures; patients >18 yrs old; outcomes of DVT, PE, fatal PE, or total mortality evaluated within standardized postoperative time; at least assessor blinding (if not double-blind)	-4 studies identified (total of 1,183 patients) -LDUH and LMWH were found equally effective in preventing DVT and/or PE (combined OR=1.01, 95%CI 0.67-1.52); test for heterogeneity non-significant	-In colorectal surgery, unfractionated heparin can be replaced with low molecular weight heparin. NOTES: this systematic review also compared heparin with placebo or no treatment and the use of compression devices (alone or in combination with heparin); authors acknowledged that protocol was violated in completing review

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

The subdivisions of this section are:

- Priority Aims and Suggested Measures
  - Measurement Specifications
- Key Implementation Recommendations
- Knowledge Resources
- Resources Available

Priority Aims and Suggested Measures

1. Increase the percentage of hospitalized adult patients (18 years and older) who are assessed for VTE risk within 24 hours of admission. *(Annotation #2)*

   Possible measure for accomplishing this aim:

   a. Percentage of hospitalized adult patients (18 years and older) who have a VTE assessment documented in the medical record. *(JCAHO/Draft Measure)*

2. Increase the percentage of patients who are evaluated for venous prophylaxis upon change in level of care, and/or upon discharge. *(Annotations #1, 2)*

   Possible measure for accomplishing this aim:

   a. Percentage of patients upon change in level of care and/or upon discharge who have documentation in their medical record that they were evaluated for venous prophylaxis.

3. Increase the percentage of hospitalized adult patients (18 years and older) who are at risk for VTE who have received education for VTE that includes VTE risk, signs and symptoms, and treatment/prophylaxis methods available within 24 hours of admission. *(Annotations #4, 5, 6, 7, 8)*

   Possible measure for accomplishing this aim:

   a. Percentage of hospitalized adult patients who are at risk for VTE who have documented education for VTE education in the medical record.

4. Increase the percentage of hospitalized adult patients who begin early and frequent ambulation. *(Annotations #4, 5, 6, 7, 8)*

   Possible measure for accomplishing this aim:

   a. Percentage of hospitalized adult patients who have documentation of early and frequent ambulation recorded in the medical record.

5. Increase the percentage of hospitalized adult patients (18 years and older) receiving appropriate prophylaxis treatment within 24 hours of admission. *(Annotations #4, 5, 6, 7, 8)*

   Possible measures for accomplishing this aim:

   a. Percentage of hospitalized adult patients with risk for VTE who receive pharmacological prophylaxis treatment, unless contraindicated. *(CMS Quality Measure)*

   b. Percentage of hospitalized adult patients with contraindications to pharmacologic prophylaxis in the medical record who receive mechanical prophylaxis. *(CMS Quality Measure)*

6. Reduce the risk of complications from pharmacologic prophylaxis. *(Annotations #3, 9)*

   Possible measures for accomplishing this aim:

   a. Percentage of hospitalized adult patients receiving heparin therapy for VTE prophylaxis who have a baseline platelet count before starting heparin, and then a platelet count every other day. *(JCAHO Draft Quality Measure)*

   b. Percentage of hospitalized adult patients with a creatinine clearance less than 30 mL/min in the medical record who receive a reduce dose of anticoagulation therapy. *(JCAHO/Draft Quality Measure)*

   c. Percentage of hospitalized adult patients who require hospital readmission within 30 days of discharge for conditions related to VTE. *(CMS Quality Measure/JCAHO Draft Quality Measure)*

7. Increase the percentage of patients who are discharged on warfarin who have an international normalized ratio (INR) within one week. *(Annotations #7, 8)*

   Possible measure for accomplishing this aim:

   a. Percentage of hospitalized patients (18 years and older) who have warfarin prior to discharge who have an international normalized ratio (INR) conducted within one week.

Measurement Specifications

Possible Success Measurement # 1a

Percentage of adult hospitalized patients who are assessed for VTE risk within 24 hours of admission. *(JCAHO/CM Quality Measure)*

Population Definition

Adults 18 and older admitted to the hospital for a medical condition or surgery.

Data of Interest

Documentation in chart of patient's VTE risk assessment based on existing risk factors.

Numerator/Denominator Definitions

Numerator: Total number of adult hospitalized patients with a completed VTE risk assessment in the medical record.

Denominator: Total number of adult patients.

Method/Source of Data Collection

From discharge records, a list of all adult patients hospitalized during the target period. The medical records can be reviewed to determine the documentation of a completed VTE risk assessment.

Time Frame Pertaining to Data Collection

Data may be collected monthly on a sample of patients (20-25/month) for process improvement purposes.

IOM Aims

Safe

Effective

Efficient

Possible Success Measurement # 5a

Percentage of adult hospitalized patients who are assessed to be at risk for VTE who receive pharmacologic prophylaxis, unless contraindicated. *(CMS Quality Measure)*

Population Definition

Adults 18 and older admitted to the hospital for a medical condition or surgery who are at risk for VTE.

Data of Interest

Documentation in chart of VTE risk and anticoagulation prophylaxis.

Numerator/Denominator Definitions

Numerator: Total number of adult hospitalized patients at risk for VTE who receive pharmacologic prophylaxis, unless contraindicated.

Denominator: Total number of adult hospitalized patients at risk for VTE.

Method/Source of Data Collection

From discharge records, a list of all adult hospitalized patients will need to be reviewed for VTE criteria during the target period. The medical records can be reviewed to determine if anticoagulation prophylaxis was administered.

Time Frame Pertaining to Data Collection

Data may be collected monthly.

IOM Aims

Safe

Effective

Efficient

Definitions

Patients are at risk for VTE if:

- admission to the ICU,
- estimated length of stay is four days or more or extended immobility exists,
- 75 years of age or more,
- thrombophilia – acquired or congenital,
- active cancer or myloproliferative disorders,
- uncompensated heart failure,
- acute infection,
- inflammatory bowl disease,
- nephrotic syndrome,
- rheumatoid/collagen vascular disorders, or
- obesity (BMI greater than or equal to 30).

Documentation of Contraindications Include But Not Limited to:

- thrombocytopenia (platelet count less than 50,000 mm_3),
- history of heparin-induced thrombocytopenia (for LMWH and UFH),
- active hepatitis or hepatic insufficiency, or
- other conditions that could increase risk of bleeding.

Possible Success Measurement # 6c

Percentage of hospitalized adult patients who require hospital readmission within 30 days of discharge for conditions related to VTE. *(CMS Quality Measure, JCAHO Draft Quality Measure)*

Population Definition

Adults 18 and older hospitalized for a medical condition or surgery.

Data of Interest

Readmission within 30 days of discharge for conditions related to VTE.

Numerator/Denominator Definitions

Numerator: Total number of hospitalized adult patients who had a previous admission within the last 30 days for conditions related to VTE.

Denominator: Total number of hospitalized adult patients.

Method/Source of Data Collection

A list of all hospitalized adult patients during the previous target period. The medical records can be reviewed to determine the documentation of readmission for conditions related to VTE.

Time Frame Pertaining to Data Collection

Data may be collected quarterly.

IOM Aims

Safe

Effective

Efficient

Timely

Key Implementation Recommendations

The following system changes were identified by the guideline work group as key strategies for health care systems to incorporate in support of the implementation of this guideline.

1. Medical groups and hospitals are encouraged to develop a formal strategy that addresses the prevention of thromboembolic complications.
    - Develop organization-specific protocols.
    - Develop documents outlining the operational steps taken when formalizing strategies around prevention of thromboembolic complications.
2. Medical groups and hospitals are encouraged to develop systems that support:
    - early identification of patients at risk for VTE development (possibly through use of order sets or similar tools);
    - appropriate prophylaxis initiation (possibly through order sets and/or anticoagulation and ambulation protocols); and
    - patient education to include documentation of the patient's own awareness of his/her risk for VTE, signs and symptoms of VTE and when/how to seek treatment, and demonstrated understanding of the prescribed anticoagulation regimen.

Knowledge Resources

Criteria for Selecting Resources

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

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

Resources Available to ICSI Members Only

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

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

Resources Available

*	Title/Description	Audience	Author/Organization	Web Sites/Order Information
	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	Anticoagulation Forum	http://www.acforum.org
	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	CareInternet	http://www.careinternet.com
	Deep Vein Thrombosis (DVT)	Patients	Park Nicollet Health Services	http://www.icsi.org/knowledge/cardiovascular Click on Patient Resources
	Single sheet describing importance of diet, helpful hints and when to call the doctor.	If You Take Coumadin®	KRAMES Communications 1998	https://shop.krames.com
	Venous Thromboembolism Prophylaxis for the Medically Ill Patient order set.	Providers	ICSI	http://www.icsi.org Select guidelines, order sets & protocols/cardiovascular

* Available to ICSI members only.