FREE CME

CLEVELAND CLINIC JOURNAL OF MEDICINE

PREVENTING VENOUS THROMBOEMBOLISM THROUGHOUT THE CONTINUUM OF CARE

SUPPLEMENT EDITOR:

AMIR K. JAFFER, MD
UNIVERSITY OF MIAMI

SUPPLEMENT TO CLEVELAND CLINIC JOURNAL OF MEDICINE
Supplement 3, Volume 75
April 2008

SUPPLEMENT
FREE CME

CONTINUING MEDICAL EDUCATION INFORMATION

Release Date: April 1, 2008
Expiration Date: April 1, 2010

Content/Overview

This activity reviews the impact of venous thromboembolism (VTE), principles of VTE risk assessment, the rationale for VTE prevention, and the pros and cons of various options for VTE prophylaxis. It focuses particularly on considerations surrounding VTE prophylaxis in three high-risk patient populations: hospitalized medical patients, patients undergoing surgery for cancer, and patients undergoing orthopedic surgery. Case studies and practical management algorithms are presented for VTE prevention in each of these three patient groups.

Statement of Need

VTE is common among hospitalized and recently discharged patients, and it has substantial clinical and economic impact. Moreover, VTE risk assessment and prophylaxis are increasingly being considered as a quality measure for health system performance ratings and reimbursement. Despite this recognition of the importance of VTE, as well as the existence of established clinical guidelines endorsing the use of VTE prophylaxis, rates of appropriate VTE prophylaxis in hospitalized and recently discharged patients are consistently low across numerous US and multinational studies. Physicians who care for hospitalized medical patients and surgical patients need practical guidance on when and for how long thromboprophylaxis is indicated for these patients, which prophylaxis options are best in various settings, and what the evidence-based risk:benefit profile of VTE prophylaxis actually is in these high-risk patient groups.

Learning Objectives

Upon completing this activity, participants will be able to:

- Recognize the burden of VTE risk in both medical and surgical patients in the inpatient and outpatient settings
- Summarize the evidence base of consensus guidelines for VTE prophylaxis and apply them to clinical practice
- Develop a VTE prophylaxis regimen for specific patient populations both during hospitalization and after discharge
- Compare and contrast the safety and efficacy of available anticoagulant therapies and their recommended use for VTE prophylaxis.

Intended Audience

This activity is intended for hospitalists, oncologists, orthopedic surgeons, internists, and other health care professionals interested in VTE prophylaxis.

Accreditation

The Cleveland Clinic Foundation Center for Continuing Education is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Cleveland Clinic Foundation Center for Continuing Education designates this educational activity for a maximum of X AMA *PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This activity may be submitted for American Osteopathic Association Continuing Medical Education credit in Category 2.

Activity Director and Supplement Editor

Amir K. Jaffer, MD
Associate Professor of Medicine
Chief, Division of Hospital Medicine
Department of Medicine
Leonard M. Miller School of Medicine
University of Miami
Miami, FL

Co-Activity Director

Franklin A. Michota, Jr., MD
Department of Hospital Medicine
Cleveland Clinic
Cleveland, OH

Faculty

Alpesh N. Amin, MD, MBA
Professor and Chief, Division of General Internal Medicine
Executive Director, Hospitalist Program
Vice Chair for Clinical Affairs & Quality, Department of Medicine
University of California, Irvine
Irvine, CA

Daniel J. Brotman, MD
Director, Hospitalist Program
Associate Professor of Medicine
Johns Hopkins Hospital
Baltimore, MD

Steven B. Deitelzweig, MD
Vice President of Medical Affairs
Chairman, Department of Hospital Medicine
Ochsner Health System
New Orleans, LA

Sylvia C. McKean, MD
Medical Director, BWH/Faulkner Hospitalist Service
Associate Professor of Medicine, Harvard Medical School and Brigham and Women's Hospital
Boston, MA

Alex C. Spyropoulos, MD
Chair, Clinical Thrombosis Center, Lovelace Medical Center
Clinical Associate Professor of Medicine/Associate Professor of Pharmacy, University of New Mexico Health Sciences Center/College of Pharmacy
Albuquerque, NM

Faculty Disclosure

In accordance with the Standards for Commercial Support issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Foundation Center for Continuing Education requires resolution of all faculty conflicts of interest to ensure CME activities are free of commercial bias.

The following faculty have indicated that they may have a relationship which, in the context of their contributions to this supplement, could be perceived as a potential conflict of interest:

Alpesh N. Amin, MD, MBA, has received research funding and honoraria for speaking from Sanofi-Aventis, Eisai, and GlaxoSmithKline.

Steven B. Deitelzweig, MD, has received honoraria for teaching/speaking from Sanofi-Aventis.

Amir K. Jaffer, MD, has received consulting fees and honoraria for teaching/speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim. He also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and on the board of directors of the Anticoagulation Forum.

Sylvia C. McKean, MD, has received honoraria for teaching/speaking from Sanofi-Aventis.

Alex C. Spyropoulos, MD, has received consulting fees from Sanofi-Aventis, Eisai, and Boehringer Ingelheim.

The following faculty indicated that they have no relationships which, in the context of their contributions to this supplement, could be perceived as a potential conflict of interest:

Daniel J. Brotman, MD
Franklin A. Michota, Jr., MD

Disclaimer

The information in this educational activity is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in this CME activity are those of the authors/faculty. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through this CME activity.

Acknowledgment

The Cleveland Clinic Foundation Center for Continuing Education acknowledges an educational grant for support of this activity from:

How to Receive *AMA PRA Category 1 Credit™*

To receive a maximum of X.X *AMA PRA Category I Credit(s)*™:

1. Read this supplement
2. Log on to **www.clevelandclinicmeded.com/XXXXXXXX**
3. Complete the post-test, evaluation, and registration form
4. Print your AMA PRA Category 1 certificate on your personal printer

System requirements: Internet Explorer 4.0 and above
Technical assistance: Call 216-297-7316 Monday–Friday 8:00 AM to 5:00 PM ET

Preventing Venous Thromboembolism Throughout the Continuum of Care

Supplement 3 to Volume 75, April 2008

www.ccjm.org/ccjm_pdfs_supplements/vte.asp

Supplement Editor

Amir K. Jaffer, MD
Leonard M. Miller School of Medicine
University of Miami

Contents

This supplement is based on the proceedings of a roundtable convened in Miami, FL, on December 1, 2007, by the Cleveland Clinic Center for Continuing Education and the Cleveland Clinic Journal of Medicine.

Topics and editors for supplements to the *Cleveland Clinic Journal of Medicine* are determined by the *Journal's* editor-in-chief and staff. Supplement editors are chosen for their expertise in the topics discussed and are responsible for the scientific quality of supplements, including the review process. The *Journal* ensures that supplement editors and authors fully disclose any relationships with industry, including the supplement underwriter. For full guidelines on grant-supported supplements to the *Journal*, go to **www.ccjm.org/instructions_grant-supported_supplements.asp.**

From the editor

Venous thromboembolism (VTE) is a disease that is under the microscope of several important organizations, including the Centers for Medicare and Medicaid Services (CMS) and the Joint Commission. It is also at the forefront of the agendas of hospital safety and quality-improvement committees. There is a push to look at both process and outcome measures with VTE, and these measures have been linked to hospital pay-for-performance programs.

This supplement is based on a recent roundtable conference in Miami, FL, that brought together six nationally renowned experts in thromboembolic disease to discuss evidence-based best practices surrounding VTE prevention. We focused on prevention in three high-risk populations: hospitalized medical patients, cancer surgery patients, and patients undergoing major joint replacement or hip fracture repair. We also discussed clinical cases and challenges as part of the roundtable discussion portions that conclude each of the three major articles in this supplement.

Our goal in developing this supplement has been to make clear the need for clinicians to focus on details of the type, dose, and duration of appropriate VTE prophylaxis both in the hospital and at discharge, with the ultimate goal of preventing a large number of patients from presenting in the outpatient setting as a result of failure to prevent VTE.

Amir K. Jaffer, MD
Leonard M. Miller School of Medicine
University of Miami, Miami, FL
ajaffer@med.miami.edu

The *Cleveland Clinic Journal of Medicine* [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published 12 times yearly by the Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal $108; institutional $134; single copy/back issue $20. Foreign: $134; single copy/back issue $20. Institutional (multiple-reader) rate applies to libraries, schools, hospitals, and federal, commercial, and private organizations. Individual subscriptions must be in the names of and paid by individuals.

Postmaster address changes: Cleveland Clinic Journal of Medicine, NA32, 9500 Euclid Avenue, Cleveland, OH 44195. Subscription orders, editorial, reprint, and production offices (same address): (216) 444-2661 (phone); (216) 444-9385 (fax); ccjm@ccf.org (e-mail); www.ccjm.org (Web).

Printed in USA.

AMIR K. JAFFER, MD

An overview of venous thromboembolism: Impact, risks, and issues in prophylaxis

ABSTRACT

Venous thromboembolism (VTE) is a major cause of cardiovascular death, and its close association with increased age portends an increasing clinical and economic impact for VTE as the US population ages. Studies show that rates of VTE prophylaxis remain inadequate both in the hospital and at the time of discharge. Health care accreditation and quality organizations are taking interest in VTE risk assessment and prophylaxis as a measure for hospital performance ratings and even reimbursement. To set the stage for the rest of this supplement, this article reviews the rationale for VTE prophylaxis, surveys current prophylaxis rates and strategies to increase those rates, and provides an overview of risk factors for VTE and therapeutic options for VTE prophylaxis.

Venous thromboembolism (VTE)—which comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE), which can result from DVT—is the third leading cause of cardiovascular death in the United States, after myocardial infarction and stroke. The annual incidence of DVT approaches 2 million.[1] Silent PE constitutes approximately half of DVT cases, as suggested by studies using ventilation perfusion scanning. The true incidence of PE is not known but is estimated to be 600,000 cases annually,[1] with approximately one third of these cases leading to death.[2]

The cost of care related to VTE in the United States has been estimated at $1.5 billion per year.[1] As an example of its economic impact on the individual patient level, an analysis of 2001–2002 cost data from a large private-sector medical center found that postoperative thromboembolic complications added an average of $18,310 to total hospital costs for each patient in whom they occurred.[3]

See inside front cover for author affiliation. See end of article for author disclosures.

Notably, the incidence of VTE rises at an exponential rate with increasing age after the second decade of life, as shown in **Figure 1**.[2] Given the aging of the US population, this suggests that the clinical and economic impact of VTE will only increase in the years ahead.

DESPITE ESTABLISHED BENEFITS, VTE PROPHYLAXIS REMAINS UNDERUSED

The frequency, clinical impact, and economic impact of VTE make a strong case for VTE prevention. In a 2001 analysis of patient safety practices, the Agency for Healthcare Research and Quality listed appropriate VTE prophylaxis in at-risk patients first in a rating of safety practices with the greatest strength of evidence for impact and effectiveness.[4]

Despite this recognition of the importance and benefit of VTE prophylaxis, prophylaxis remains highly underutilized. This has been demonstrated in numerous studies; the large epidemiologic investigation by Goldhaber et al using the DVT Free Registry is illustrative.[5] This prospective multicenter study enrolled 5,451 consecutive patients with acute DVT documented by venous ultrasonography over a 6-month period. Patients were classified as either outpatients or inpatients: outpatients were those who came to the emergency room and were diagnosed with DVT; inpatients were those who developed DVT in the hospital. Of the 2,726 inpatients in the registry, only 42% had received prophylaxis within 30 days prior to their diagnosis of DVT.

Risk extends to the outpatient setting

In a recent population-based analysis, Spencer et al found a similarly low rate of VTE prophylaxis—42.8%—among 516 patients who had recently been hospitalized and subsequently developed VTE.[6] This study also found that VTE was three times as likely in the outpatient setting as in the inpatient setting, and that almost half of the outpatients with VTE had been recently hospitalized. Taken together, these findings indicate that VTE prevention efforts are inadequate

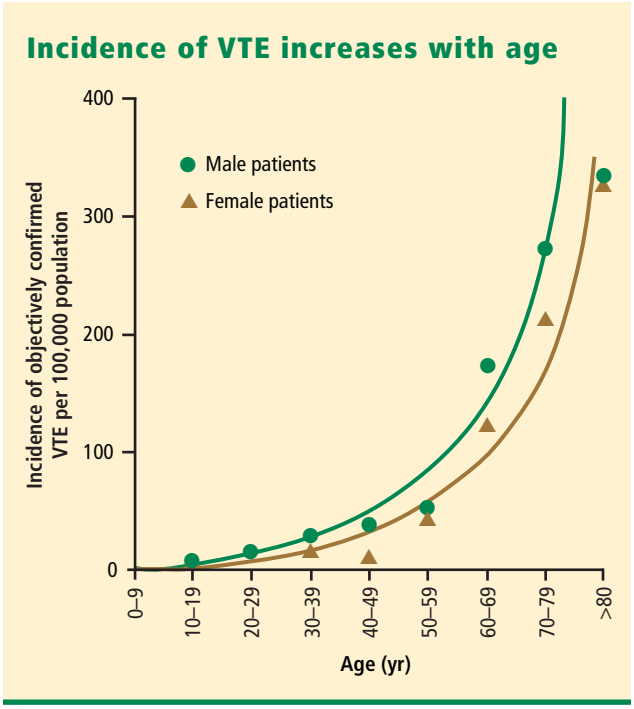


FIGURE 1. Incidence rates of venous thromboembolism (VTE) per 100,000 population for men and women in the population-based Worcester DVT Study.[2] The increase in incidence for both sexes is well approximated by an exponential function of age.

both in the hospital and at the time of discharge, when patients' risk for VTE is still elevated.[6,7]

VTE PROPHYLAXIS AS AN EMERGING QUALITY MEASURE

Increased recognition of the impact of VTE has prompted accreditation and quality organizations to take interest in VTE risk assessment and prophylaxis as a measure for institutional performance ratings and even reimbursement.

The Joint Commission on Accreditation of Healthcare Organizations and the National Quality Forum have launched a joint project to develop a set of standardized inpatient measures to evaluate hospitals' practices for the prevention and treatment of VTE.[8] The project has pilot-tested several proposed performance measures in dozens of volunteer hospitals, including measures of whether VTE risk assessment is performed and VTE prophylaxis is initiated (if indicated) within 24 hours of admission to the hospital or to the intensive care unit. Hospitals participating in the pilot program are required to report their rates of potentially preventable hospital-acquired VTE.

Similarly, the ongoing Surgical Care Improvement Project (SCIP) has targeted VTE prophylaxis as one of a handful of priority areas for reducing surgical complications. As a national quality partnership of organizations sponsored by the Centers for Medicare and Medicaid Services (CMS), SCIP set a national goal in 2005 to reduce preventable surgical morbidity and mortality by 25% by 2010.[9]

The stakes of the SCIP initiative are high in both clinical and financial terms. CMS mandated that hospitals report on three SCIP quality measures in 2007 in order to receive full Medicare reimbursement in 2008. Of the three measures, two involved VTE prophylaxis: (1) how often VTE prophylaxis was ordered for surgical patients when indicated, and (2) how often appropriate surgical patients received prophylaxis postoperatively. Moreover, beginning October 1, 2008, CMS will no longer reimburse hospitals for certain preventable conditions, and DVT and PE are being considered for inclusion in this list of conditions excluded from reimbursement.[10]

PROPHYLAXIS RATES CAN BE IMPROVED

Fortunately, there is evidence that interventions to increase awareness may increase the rate of VTE prophylaxis. Stinnett et al reported that education, in the form of hospital-specific data on VTE rates and implementation of risk-stratification guidelines, increased the use of VTE prophylaxis in high-risk hospitalized medical patients at a tertiary care center from a preintervention rate of 43% to a postintervention rate of 72%.[11]

In addition to educational interventions, formalized risk-assessment tools, in the form of electronic alerts, offer another strategy that may increase rates of VTE prophylaxis. The promise of this approach was demonstrated in a study at Brigham and Women's Hospital in Boston, in which 2,506 hospitalized patients at risk for VTE were randomly assigned to either an intervention group, in which physicians received a computer alert about the patient's VTE risk, or a control group, in which no alert was issued.[12] The rate of VTE prophylaxis was more than twice as high in the intervention group as in the control group (33.5% vs 14.5%; $P < .001$), and the 90-day incidence of VTE was reduced from 8.2% in the control group to 4.9% in the intervention group ($P = .001$).

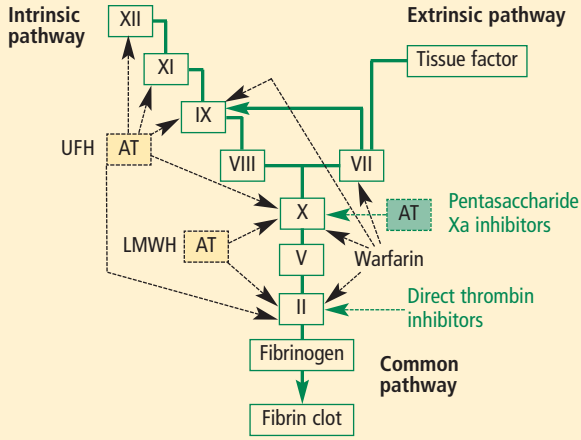
WHO'S AT RISK FOR VTE?

Our understanding of the risk factors for VTE dates back more than a century to the work of the German pathologist Rudolf Virchow, who identified three broad categories of risk: circulatory stasis, endothelial

TABLE 1
Risk factors for VTE

Surgery	Infection
Trauma	Heart failure
Immobility, paresis	Respiratory failure
Malignancy	Inflammatory bowel disease
Cancer therapy (hormonal chemotherapy or radiotherapy)	Nephrotic syndrome
Previous VTE	Myeloproliferative disorders
Increased age (especially > 75 yr)	Obesity
Pregnancy and postpartum status	Smoking
Estrogen-containing oral contraception, or HRT or SERM therapy	Varicose veins
	Central venous catheterization
	Inherited/acquired thrombophilia
	Travel

VTE = venous thromboembolism; HRT = hormone replacement therapy; SERM = selective estrogen receptor modulator



AT = antithrombin; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin
Roman numerals represent clotting factors.

FIGURE 2. The pathways of coagulation and the points of action of various classes of anticoagulant therapies.

Reprinted from Nutescu EA, et al. A pharmacologic overview of current and emerging anticoagulants. Cleve Clin J Med 2005; 72(Suppl 1):S2 S6.

injury, and hypercoagulable state. These categories manifest as a multiplicity of specific risk factors, as outlined in **Table 1**. Notably, many of these risk factors are highly prevalent in hospitalized patients. Also particularly notable is the association between increasing age and VTE, as illustrated in **Figure 1**.

OPTIONS FOR VTE PROPHYLAXIS

An ideal therapy for VTE prophylaxis would be one that is effective, safe, inexpensive, and easy to administer and monitor, and that has few side effects or complications.

Mechanical prophylaxis

Mechanical forms of VTE prevention carry no risk of bleeding, are inexpensive because they can be reused, and are often effective when used properly. Mechanical forms include graduated compression stockings, intermittent pneumatic compression devices, and venous foot pumps.

The American College of Chest Physicians (ACCP), in its Seventh ACCP Conference on Antithrombotic Therapy and Thrombolytic Therapy, published in 2004,[13] recommends that mechanical methods be used primarily in two settings:

- In patients with a high risk of bleeding (in whom pharmacologic prophylaxis is contraindicated)
- As an adjunct to pharmacologic prophylaxis.

Because the use of mechanical forms of prophylaxis in hospitalized medical patients is not evidence-based, mechanical prophylaxis should be reserved for those medical patients at risk for VTE who have a contraindication to pharmacologic prophylaxis.

To be effective, mechanical forms of prophylaxis must be used in accordance with the device manufacturer's guidelines, which is frequently not what happens in clinical practice. In clinical trials in which the efficacy of intermittent pneumatic compression devices was demonstrated, patients wore their devices for 14 to 15 hours per day.

Pharmacologic options

The pharmacologic options for prevention of VTE act at different points in the coagulation cascade **(Figure 2)**, as detailed below.

Unfractionated heparin (UFH) inhibits factor Xa and factor IIa equally. Because it is a large heterogeneous molecule, UFH is not well absorbed in subcutaneous tissue. Its anticoagulant response is variable because of its short half-life. It must be dosed two or three times daily subcutaneously for VTE prophylaxis, and must be given intravenously for treatment of VTE. The rate of heparin-induced thrombocytopenia, a potentially catastrophic adverse drug event, is considerably higher with UFH than with low-molecular-weight heparins (3% vs 1%).[14] Osteopenia can develop with the use of UFH over even short periods, and osteoporosis can occur with long-term use.

Low-molecular-weight heparins (LMWHs) preferentially inhibit factor Xa compared to factor IIa. The LMWHs (ie, enoxaparin [Lovenox], dalteparin [Frag-

min]) are derived from UFH through a chemical depolymerization and defractionation process that results in a much smaller molecule. LMWHs are well absorbed from subcutaneous tissue and have a predictable dose response attributable to their longer half-life (relative to UFH), which allows for once-daily or twice-daily subcutaneous dosing. As noted above, LMWHs carry a much lower rate of heparin-induced thrombocytopenia compared with UFH. Because LMWHs are predominantly cleared by the kidneys, dose adjustment may be needed in patients with renal impairment.

Fondaparinux (Arixtra) is a synthetic pentasaccharide that acts as a pure inhibitor of factor Xa. It binds antithrombin III, causing a conformational change by which it inhibits factor Xa and thereby inhibits coagulation further downstream. Fondaparinux has a long half-life (18 to 19 hours), which enables once-daily subcutaneous dosing but which also may require administration of the costly activated factor VII (NovoSeven) to reverse its effects in cases of bleeding. Because fondaparinux is cleared entirely by the kidneys, it is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min). It is also contraindicated in patients who weigh less than 50 kg, due to increased bleeding risk.

Details on the efficacy of these agents for VTE prophylaxis in various patient groups are provided in the subsequent articles in this supplement.

Investigational anticoagulants

The above pharmacologic options may soon be joined by several experimental anticoagulants that are currently in phase 3 trials for VTE prophylaxis—oral factor Xa inhibitors such as rivaroxaban and apixaban, and oral factor IIa (thrombin) inhibitors such as dabigatran.

AUTHOR DISCLOSURES

Dr. Jaffer reported that he has received consulting fees and honoraria for teaching/speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim. He also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and the board of directors of the Anticoagulation Forum.

Dr. Jaffer received an honorarium for participating in the roundtable that formed the basis of this supplement. The honorarium was paid by the Cleveland Clinic Center for Continuing Education from the educational grant from Sanofi-Aventis underwriting this supplement. Sanofi-Aventis had no input on the content of the roundtable or this supplement.

REFERENCES

1. **Hirsh J, Hoak J.** Management of deep vein thrombosis and pulmonary embolism. A statement for healthcare professionals from the Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. Circulation 1996; 93:2212–2245.
2. **Anderson FA Jr, Wheeler HB, Goldberg RJ, et al.** A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991; 151:933–938.
3. **Dimick JB, Chen SL, Taheri PA, Henderson WG, Khuri SF, Campbell DA Jr.** Hospital costs associated with surgical complications: a report from the private-sector National Surgical Quality Improvement Program. J Am Coll Surg 2004; 199:531–537.
4. **Agency for Healthcare Research and Quality.** Making Health Care Safer: A Critical Analysis of Patient Safety Practices. Evidence Report/Technology/Assessment: Number 43. AHRQ Publication No. 01-E058. Rockville, MD: Agency for Healthcare Research and Quality; July 2001:620. http://www.ahrq.gov/clinic/ptsafety/. Accessed December 4, 2007.
5. **Goldhaber SZ, Tapson VF; DVT FREE Steering Committee.** A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. Am J Cardiol 2004; 93:259–262.
6. **Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ.** Venous thromboembolism in the outpatient setting. Arch Intern Med 2007; 167:1471–1475.
7. **Goldhaber SZ.** Outpatient venous thromboembolism: a common but often preventable public health threat. Arch Intern Med 2007; 167:1451–1452.
8. National Consensus Standards for Prevention and Care of Venous Thromboembolism (VTE). The Joint Commission Web site. http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/VTE.htm. Accessed January 8, 2008.
9. Surgical Care Improvement Project. MedQIC Web site. http://www.medqic.org/scip/. Accessed January 8, 2008.
10. **US Department of Health and Human Services.** Medicare program; changes to the hospital inpatient prospective payment systems and fiscal year 2008 rates. http://www.cms.hhs.gov/AcuteInpatientPPS/downloads/CMS-1533-FC.pdf. Accessed December 4, 2007.
11. **Stinnett JM, Pendleton R, Skordos L, Wheeler M, Rodgers GM.** Venous thromboembolism prophylaxis in medically ill patients and the development of strategies to improve prophylaxis rates. Am J Hematol 2005; 78:167–172.
12. **Kucher N, Koo S, Quiroz R, et al.** Electronic alerts to prevent venous thromboembolism among hospitalized patients. N Engl J Med 2005; 352:969–977.
13. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):338S–400S.
14. **Warkentin TE, Levine MN, Hirsh J, et al.** Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335.

Correspondence: *Amir K. Jaffer, MD, Chief, Division of Hospital Medicine, Leonard M. Miller School of Medicine, University of Miami, 1120 NW 14th Street, 933 CRB (C216), Miami, FL 33136; ajaffer@med.miami.edu.*

AMIR K. JAFFER, MD ALPESH N. AMIN, MD, MBA DANIEL J. BROTMAN, MD
STEVEN B. DEITELZWEIG, MD SYLVIA C. McKEAN, MD ALEX C. SPYROPOULOS, MD

Prevention of venous thromboembolism in the hospitalized medical patient

ABSTRACT

Hospitalized acutely ill medical patients are at high risk for venous thromboembolism (VTE), and clinical trials clearly demonstrate that pharmacologic prophylaxis of VTE for up to 14 days significantly reduces the incidence of VTE in this population. Guidelines recommend use of low-molecular-weight heparin (LMWH) or unfractionated heparin (5,000 U three times daily) for VTE prophylaxis in hospitalized medical patients with risk factors for VTE; in patients with contraindications to anticoagulants, mechanical prophylaxis is recommended. All hospitalized medical patients should be assessed for their risk of VTE at admission and daily thereafter, and those with reduced mobility and one or more other VTE risk factors are candidates for aggressive VTE prophylaxis. Based on results from the recently reported EXCLAIM trial, extended post-discharge prophylaxis with LMWH for 28 days should be considered for hospitalized medical patients with reduced mobility who are older than age 75 or have a cancer diagnosis or a history of VTE.

The need for prophylaxis of venous thromboembolism (VTE) in hospitalized acutely ill medical patients is well established. Without prophylaxis, hospitalized medical patients develop VTE at a rate of 5% to 15%.[1–3] Moreover, pulmonary embolism (PE) occurs more frequently in hospitalized medical patients than in nonmedical patients, and is a leading cause of sudden death in hospitalized medical patients.[4,5] Without appropriate prophylaxis, 1 in 20 hospitalized medical patients may suffer a fatal PE.[4]

PROPHYLAXIS IN MEDICAL PATIENTS: UNDERUSED AND OFTEN INAPPROPRIATE

Despite these risks and the clear indications for VTE prophylaxis in hospitalized medical patients, prophylaxis of VTE is omitted more often in these patients than in hospitalized surgical patients.[5] Even when prophylaxis is given, it is often used inappropriately in the medical population. So concludes a recent analysis of data from 196,104 patients with acute medical conditions who were discharged from 227 US hospitals from January 2002 to September 2005.[6] Criteria for inclusion in the analysis were patient age of 40 years or older, a hospital stay of 6 days or greater, and an absence of contraindications to anticoagulation. Appropriate prophylaxis was defined in accordance with the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy.[7]

The analysis revealed an overall VTE prophylaxis rate of 61.8%, but the rate of appropriate prophylaxis was only 33.9%, meaning that two-thirds of discharged patients did not receive prophylaxis in accordance with ACCP guidelines. When temporal trends were analyzed according to groups based on patients' diagnosis at admission (acute myocardial infarction, severe lung disease, ischemic stroke, cancer, heart failure, or trauma), the rate of appropriate prophylaxis remained essentially flat from the beginning to the end of the study period for virtually all diagnosis groups.[6]

Similar findings have emerged from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE), an ongoing international registry of acutely ill medical patients.[8] Data from the first 15,156 patients, enrolled from July 2002 through September 2006, reveal that 50% of patients received pharmacologic and/or mechanical VTE prophylaxis in the hospital, and only 60% of patients who met established criteria for VTE prophylaxis actually received it.

Analysis of the US portion of the IMPROVE data shows that 54% of the US patient sample received some form of VTE prophylaxis; 22% of US patients received intermittent pneumatic compression, 21% received unfractionated heparin (UFH), 14% received

See inside front cover for author affiliations. See end of article for author disclosures.

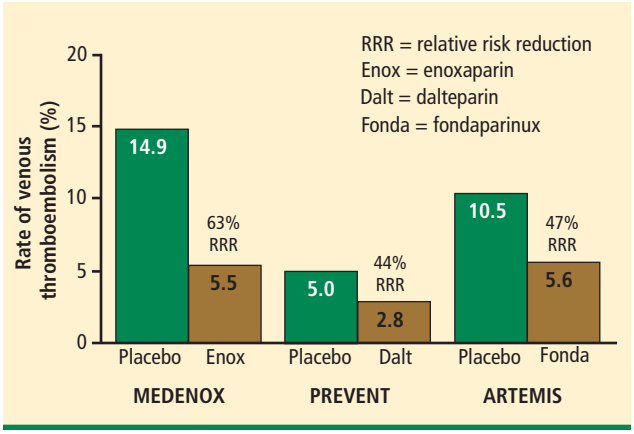


FIGURE 1. Rates of venous thromboembolism (VTE) in three large double-blind, placebo-controlled studies of pharmacologic prophylaxis of VTE in high-risk hospitalized medical patients.

low-molecular-weight heparin (LMWH), and 3% wore compression stockings.[8] Thus, despite a paucity of data supporting a benefit of intermittent pneumatic compression in this population,[9] it was the most frequently used form of prophylaxis in US patients.

CLINICAL TRIALS OF PHARMACOLOGIC PROPHYLAXIS IN MEDICAL PATIENTS

The evidence in support of pharmacologic prophylaxis of VTE in high-risk hospitalized medical patients is considerable. Three large double-blind, placebo-controlled trials of anticoagulants currently available in the United States have been reported in this patient population **(Figure 1)**.[1–3]

The Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial[1] randomized 1,102 hospitalized patients to one of two doses of the LMWH enoxaparin (20 mg or 40 mg once daily subcutaneously) or placebo for 6 to 14 days. Compared with placebo, the 40-mg dose of enoxaparin was associated with a 63% reduction in risk of VTE over 3 months of follow-up ($P < .001$) **(Figure 1)**.

The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT)[2] was a multicenter, randomized, double-blind study comparing the LMWH dalteparin (5,000 IU daily given subcutaneously for 14 days) with placebo in 3,706 acutely ill medical patients. Over 90 days of follow-up, the risk of VTE was reduced by 44% in patients assigned to dalteparin compared with those assigned to placebo ($P = .0015$) **(Figure 1)**.

The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)[3] randomized 849 medical patients 60 years or older to 6 to 14 days of therapy with the selective factor Xa inhibitor fondaparinux (2.5 mg once daily subcutaneously) or placebo. Compared with the placebo group, fondaparinux recipients had a 47% lower risk of developing VTE by day 15 ($P = .029$) **(Figure 1)**.

Fewer events and fatal PEs, but no effect on all-cause mortality

A recent meta-analysis by Dentali et al[10] further demonstrates the efficacy of anticoagulant therapy for preventing symptomatic VTE in hospitalized medical patients. This analysis included several other trials in addition to the three reviewed above,[1–3] for a total of nine randomized studies (seven of which were double-blind) comprising 19,958 patients. Across the nine studies, anticoagulant prophylaxis was clearly superior to placebo in preventing fatal PE (relative risk, 0.38 [95% CI, 0.21 to 0.69]). There was a strong trend toward a reduction in symptomatic deep vein thrombosis (DVT) with prophylaxis but no effect on all-cause mortality. The meta-analysis also provided reassurance that prophylaxis does not increase the rate of major bleeding.

HOW DO THE PROPHYLAXIS OPTIONS STACK UP?

What the ACCP recommends

Current ACCP guidelines recommend the use of either LMWH or low-dose UFH (5,000 U subcutaneously two or three times daily) as a grade 1A recommendation for VTE prophylaxis in patients with medical conditions and risk factors for VTE.[9] This represents the guidelines' highest level of recommendation, ie, one that is based on randomized controlled trials (RCTs) without important limitations. In contrast, the 2006 International Consensus Statement, developed as a collaborative effort among expert bodies on VTE, specified a more narrow dosing recommendation for UFH in this patient population (5,000 U three times daily, *not* twice daily) as well as specifying 40 mg once daily as the recommended dose of enoxaparin and 5,000 IU once daily as the recommended dose of dalteparin.[11]

For medical patients with risk factors for VTE who have a contraindication to anticoagulant prophylaxis, the ACCP guidelines recommend the use of graduated compression stockings or intermittent pneumatic compression devices as a grade 1C+ recommendation ("no RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies"[9]).

The ACCP guidelines do not address the use of fondaparinux in their recommendations for VTE prophylaxis in medical patients.

Getting a handle on bleeding risk

Patient characteristics that exclude pharmacologic thromboprophylaxis due to bleeding risk are generally limited to active bleeding or coagulopathy, as demonstrated by a platelet count less than 50,000 cells/μL or an international normalized ratio greater than 1.5. Additionally, bleeding risk should be carefully assessed if an invasive procedure is planned during a patient's hospital stay.

It is worth noting that the anticoagulant doses used for VTE prophylaxis are a fraction of those used for treatment of VTE. Thus, if a patient would be treated with full-dose anticoagulation if VTE developed, then that patient should be eligible for VTE prophylaxis.

Because the use of mechanical forms of prophylaxis in medical patients is not truly evidence-based, mechanical prophylaxis should be reserved for medical patients who have a contraindication to anticoagulants, or for use in combination with anticoagulants in patients at very high risk of VTE.

UFH vs LMWH

Two meta-analyses have compared UFH with LMWH for VTE prevention in medical patients.[12,13] In a recent analysis that included 10 trials directly comparing the two therapies, 14 trials comparing UFH with control, and 11 trials comparing LMWH with control, Wein et al found a lower risk of DVT with LMWH than with UFH (relative risk, 0.68 [95% CI, 0.52 to 0.88]) but no difference between the therapies in mortality or bleeding risk.[12] In an earlier and smaller analysis, Mismetti et al found no significant differences between UFH and LMWH in preventing DVT or death but did find a significant reduction in major bleeding episodes with LMWH versus three-times-daily UFH (52% relative reduction; $P = .049$).[13]

Randomized trials also reveal that enoxaparin 40 mg once daily is as efficacious as UFH 5,000 U three times daily for VTE prevention in medical patients.[14,15] The above analysis by Wein et al[12] and an additional meta-analysis by King and colleagues[16] found that three-times-daily dosing of UFH is more efficacious than twice-daily dosing of UFH, but at the expense of more bleeding, including major bleeding.

Economic considerations

Because of differences in drug acquisition costs between UFH and the LMWH agents, several economic evaluations have compared the use of these therapies for prophylaxis in medical patients at risk of VTE.

In an analysis of hospital costs for medical patients receiving VTE prophylaxis from more than 330 US hospitals for the period 2001–2004, Burleigh et al found that mean total hospital costs were higher for patients who received UFH than for those who received LMWH ($7,615 vs $6,866) even though mean drug costs were higher for LMWH ($791 vs $569 for UFH).[17] A reduction in hospital length of stay appeared to contribute to the overall savings with LMWH; other contributors may have included costs associated with heparin-induced thrombocytopenia (HIT) in UFH recipients or the extra nursing time required for administering UFH in two or three daily doses.

Leykum et al used a decision analysis model to estimate the economic effect of substituting enoxaparin for UFH in hospitalized medical patients for whom VTE prophylaxis is indicated.[18] Cost data were based on Medicare reimbursement rates as well as drug and laboratory costs for a multi-institutional health system. The model assumed HIT incidence rates of 2.7% with UFH and 0.3% with enoxaparin. It also assumed the cost of a daily dose to be $4 for UFH versus $84 for enoxaparin. From the payer perspective, the model showed that substituting enoxaparin for UFH would reduce the overall cost of care by $28.61 per day on a per-patient basis, despite enoxaparin's higher acquisition cost, and would save $4,550 per quality-adjusted life-year by reducing the incidence of HIT.

Another cost analysis confirms the association between HIT and increased hospital costs. Creekmore et al retrospectively analyzed data from 10,121 adult medical patients who received VTE prophylaxis at the University of Utah Hospital in Salt Lake City from August 2000 to November 2004.[19] They found that an admission during which HIT developed incurred a mean cost of $56,364, compared with $15,231 for an admission without HIT. Because LMWH was associated with a lower incidence of HIT compared with UFH (0.084% vs 0.51%, respectively), LMWH reduced the incremental cost of VTE prophylaxis by $13.88 per patient compared with UFH.

THE EXCLAIM TRIAL: IS THERE A ROLE FOR EXTENDED PROPHYLAXIS?

Although the previously discussed studies have clearly demonstrated the benefit of in-hospital VTE prophylaxis for acutely ill medical patients, none has rigorously examined extended-duration out-of-hospital prophylaxis in these patients. This represents an important gap in the literature, since a substantial

TABLE 1
Primary efficacy outcomes in EXCLAIM trial at end of extended-duration prophylaxis period[21]

	Incidence		Relative reduction	*P* for difference
	Placebo	Enoxaparin		
Overall VTE events	4.9%	2.8%	44%	.0011
Asymptomatic proximal DVT	3.7%	2.5%	34%	.0319
Symptomatic VTE	1.1%	0.3%	73%	.0044
PE	0.2%	0%	—	NS
Fatal PE	0.1%	0%	—	NS

VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism; NS = not significant

proportion of VTE develops in the outpatient setting within 3 months of a hospitalization, and most outpatient VTE episodes occur within 1 month of a preceding hospitalization.[20]

To begin to fill this gap, the Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) trial was conducted to compare extended-duration LMWH prophylaxis with a standard LMWH prophylaxis regimen in acutely ill medical patients using a prospective, multicenter, randomized, double-blind, placebo-controlled design.[21]

Patients and study design

Patients were eligible for enrollment if they were aged 40 years or older and had recent immobilization (≤ 3 days), a predefined acute medical illness, and either level 1 mobility (total bed rest or sedentary state) or level 2 mobility (level 1 with bathroom privileges). The predefined acute medical illnesses consisted of New York Heart Association class III/IV heart failure, acute respiratory insufficiency, or other acute medical conditions, including post-acute ischemic stroke, acute infection without septic shock, and active cancer.

All patients received open-label enoxaparin 40 mg subcutaneously once daily for 10 ± 4 days, after which they were randomized to either enoxaparin 40 mg subcutaneously once daily or placebo for an additional 28 ± 4 days.

The primary efficacy end point was the incidence of VTE events, defined as asymptomatic DVT documented by mandatory ultrasonography at the end of the double-blind treatment period (28 ± 4 days) or as symptomatic DVT, symptomatic PE, or fatal PE at any time during the double-blind period. Symptomatic DVT was confirmed by objective tests; PE was confirmed by ventilation-perfusion scan, computed tomography, angiography, or autopsy.

Secondary efficacy end points were mortality at the end of the double-blind period, at 3 months, and at 6 months, as well as the incidence of VTE at 3 months.

The primary safety outcome measure was the incidence of major hemorrhage during the double-blind period; secondary safety measures were rates of major and minor hemorrhage, minor hemorrhage, HIT, and serious adverse events.

Population amended at planned interim analysis

After approximately half of the patients were enrolled, a planned and blinded interim analysis for futility concluded that the study was unlikely to show a statistically significant advantage of enoxaparin over placebo. The trial's steering committee followed the suggestion of its data safety monitoring board to redefine the inclusion criteria to refocus enrollment on patients with a high risk of VTE. A blinded analysis was performed to identify this subgroup.

The resulting amended inclusion criteria were the same as above except that level 2 mobility had to be accompanied by at least one of three additional high-risk criteria: (1) age greater than 75 years, (2) history of VTE, or (3) diagnosis of cancer.

The trial's main exclusion criteria were evidence of active bleeding, a contraindication to anticoagulation, receipt of prophylactic LMWH or UFH more than 72 hours prior to enrollment, treatment with an oral anticoagulant within 72 hours of enrollment, major surgery within the prior 3 months, cerebral stroke with bleeding, and persistent renal failure (creatinine clearance < 30 mL/min).

Results

The amended study population included 5,105 patients, 5,049 of whom received open-label enoxaparin. Of this group, 2,013 were randomized to active extended prophylaxis with enoxparain and 2,027 to placebo. Baseline characteristics, including level of mobility, were similar between the two groups.

Efficacy. As detailed in **Table 1**, VTE events occurred at a statistically significantly higher rate in the placebo arm than in the extended-duration enoxaparin arm, as did asymptomatic proximal DVT and symptomatic VTE. Rates of PE and fatal PE were also lower with enoxaparin than with placebo, but the number of events was so small that the between-

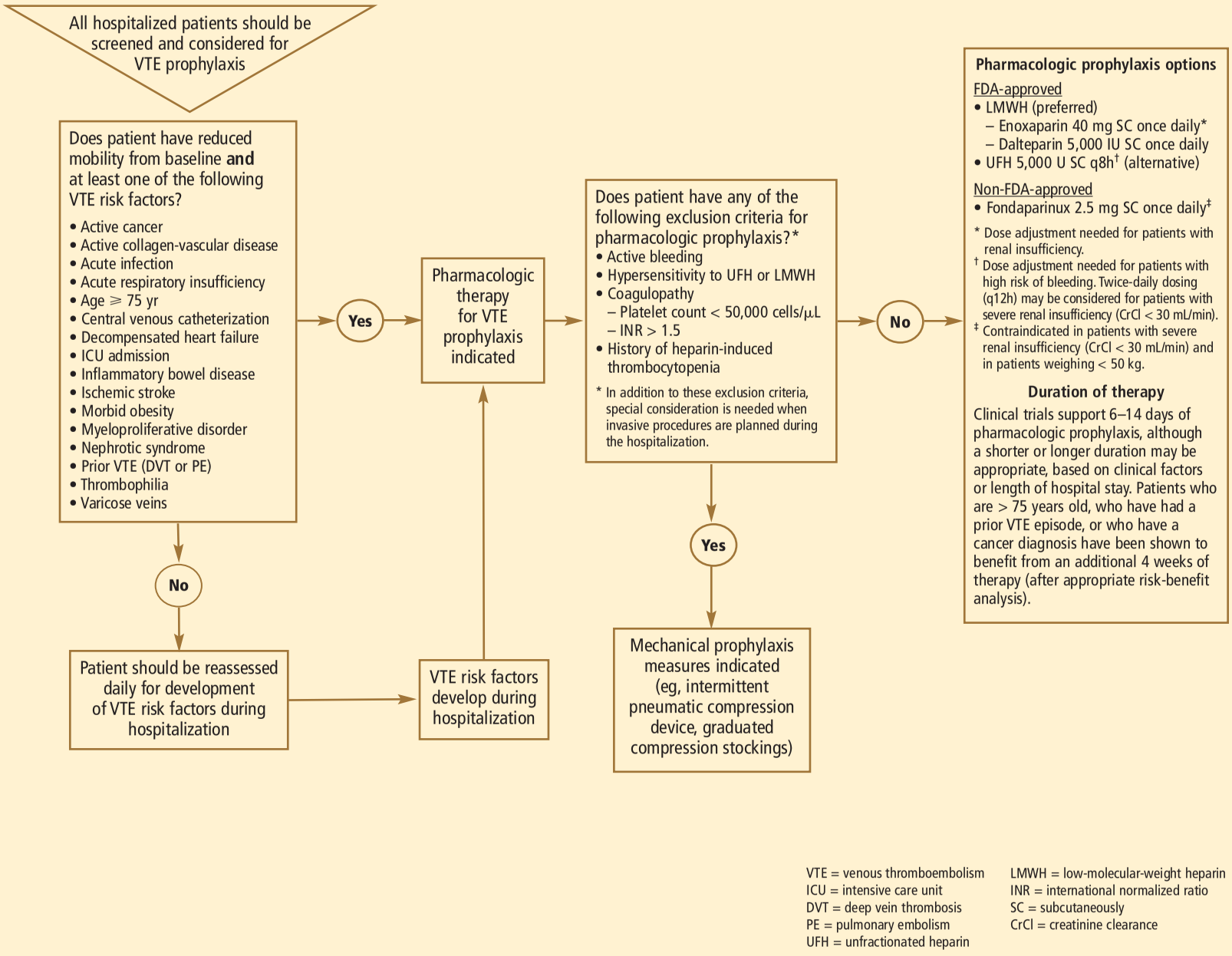


FIGURE 2. Algorithm for VTE prophylaxis in the hospitalized medical patient.

Case study: A 76-year-old woman with sepsis and heart failure

A 76-year-old woman is admitted and treated in the hospital for sepsis from a urinary source. She is sedentary while in the hospital but has no known risk factors for bleeding.

Her medical history consists of congestive heart failure (ejection fraction of 20% based on an echocardiogram obtained 1 month ago). She has no surgical history.

Her medications prior to admission were furosemide 20 mg twice daily, benazepril 40 mg/day, and carvedilol 12.5 mg/day. She has no known allergies. She reports no history of tobacco, alcohol, or illicit drug use.

Her laboratory values, which include platelets, hemoglobin, hematocrit, and creatinine, are all within the normal range except for an elevated white blood cell count of 15 on admission, which improves to normal over the course of her hospital stay.

She recovers well after 4-day treatment for urinary sepsis and heart failure with appropriate antibiotics and properly titrated fluids. She is ready for safe discharge on the fifth day of hospitalization but is still not at her baseline level of activity.

IS THIS PATIENT AT RISK FOR VTE?

Risk-factor assessment reveals that this patient has four risk factors for VTE:

- **Age greater than 75 years.** Older age, even on its own, is a significant risk factor for VTE. After the second decade of life, the risk of VTE increases exponentially in both men and women.[25]
- **History of congestive heart failure (CHF).** In a retrospective case-control study, an ejection fraction less than 20% was associated with an odds ratio for VTE of 38.3.[26]
- **Infectious etiology for her hospitalization (sepsis from urinary source).** In the first 2 weeks following an acute urinary tract infection, the risk of DVT is doubled.[27]
- **Sedentary state in the hospital and at discharge.** In the MEDENOX trial, immobilized patients who received no prophylaxis (placebo) had a VTE incidence rate of 20.3%.[28]

The presence of multiple VTE risk factors in hospitalized patients is becoming the norm. The risk for VTE increases as the number of risk factors increases, such that nearly all hospitalized patients with five or more risk factors will have the potential to develop DVT if adequate prophylaxis is not used.[29]

Without prophylaxis, the incidence of VTE in subjects enrolled in the MEDENOX trial who had the individual risk factors seen in this patient ranged from 14.6% (for acute heart failure) to 15.5% (for acute infectious disease) to 18.4% (for age > 75 years) to 20.3% (for immobility).[28] Therefore, this patient has, at minimum, a 15% to 20% likelihood of developing VTE without prophylaxis, based on any single risk factor, and most likely a much higher risk given her multiple risk factors.

WHAT IS THE APPROPRIATE PROPHYLAXIS?

The FDA-approved options for prevention of VTE are LMWH, UFH, and mechanical devices. As noted in the main text, current ACCP guidelines give preference to LMWH and low-dose UFH for VTE prophylaxis in medical patients; for patients with a contraindication to anticoagulants **(see Figure 2)**, graduated compression stockings or intermittent pneumatic compression devices are recommended.[9]

Our patient has CHF and an infectious etiology for her hospital admission. In the MEDENOX trial, prophylaxis with LMWH significantly reduced the 14-day incidence of VTE compared with placebo in patients with acute heart failure ($P = .02$) or acute infectious disease ($P = .01$).[1,28] The risk of major bleeding with pharmacologic prophylaxis in medical patients is minimal, according to the meta-analysis of Dentali et al.[10] Our patient, therefore, seems likely to benefit from pharmacologic prophylaxis given that she has no known contraindications.

Choice of anticoagulant

In choosing between LMWH and UFH, the efficacy of each in preventing DVT and the risks of bleeding and development of HIT must be considered.

As reviewed in the main text, two meta-analyses comparing UFH and LMWH for prophylaxis in medical

group differences were not statistically significant.

The efficacy of extended prophylaxis with enoxaparin was enduring, as the cumulative incidence of VTE events at day 90 was significantly lower in enoxaparin recipients than in placebo recipients (3.0% vs 5.2%; relative reduction of 42%; $P = .0115$).

There was no difference in all-cause mortality at 6 months between the enoxaparin and placebo groups (10.1% vs 8.9%, respectively; $P = .179$).

Safety. Major hemorrhage was significantly more frequent in the enoxaparin arm, occurring in 0.60% of enoxaparin recipients compared with 0.15% of placebo recipients ($P = .019$). Minor bleeding was also more common with enoxaparin (5.20% vs 3.70%; $P = .024$).

Conclusions

The EXCLAIM trial found that an extended-duration (38-day) enoxaparin regimen significantly reduced the overall incidence of VTE relative to a 10-day enoxaparin regimen in acutely ill medical patients with reduced mobility. At the same time, the extended regimen was associated with a significant increase in the

patients yielded results favorable to LMWH: Wein et al found significantly lower rates of DVT with LMWH but no difference in bleeding risk,[12] and Mismetti et al found a nonsignificant reduction in DVT rates but a significantly lower risk of bleeding with LMWH.[13] Neither analysis found differences in mortality between UFH and LMWH.

The outcomes of HIT are significant. Among patients who receive treatment for HIT, new thrombosis occurs in 10% to 20%, amputation is necessary in 5% to 15%, and death occurs in 10% to 20%.[30] Few studies have evaluated rates of HIT with thromboprophylaxis in medical patients, but a meta-analysis evaluating HIT rates in 15 clinical trials directly comparing LMWH with UFH for thromboprophylaxis, mostly in surgical patients, found that the incidence of HIT was more than 10 times higher with UFH than with LMWH (2.6% vs 0.2%).[31]

Thus, this 76-year-old woman with four risk factors for VTE and no contraindications to anticoagulants should receive prophylaxis with either LMWH or three-times-daily low-dose UFH. LMWH is preferred, given its association with lower rates of DVT in the meta-analysis by Wein et al,[12] its association with lower bleeding risk in the meta-analysis by Mismetti et al,[13] its lower incidence of HIT, and its once-daily dosing.

IS EXTENDED PROPHYLAXIS INDICATED?

Should this patient be offered out-of-hospital extended prophylaxis? If so, for how many days?

In the EXCLAIM trial, which evaluated 28 days of extended prophylaxis following discharge, 1-month rates of VTE, proximal DVT, and symptomatic VTE were 44% lower, 34% lower, and 73% lower, respectively, in patients who received extended prophylaxis with LMWH relative to those who did not.[21] When the EXCLAIM results were analyzed by patients' primary diagnosis at study entry, extended prophylaxis was associated with a 36% relative reduction in the risk of VTE among patients with a primary diagnosis of heart failure and a 34% relative reduction among patients with acute infectious disease as a primary diagnosis.

The EXCLAIM investigators concluded that the number needed to treat with extended prophylaxis to prevent one VTE event is much smaller than the number needed to harm in terms of major bleeding (46 vs 224). This, together with the fact that age greater than 75 years was one of the trial's amended entry criteria, supports consideration of 28 days of extended prophylaxis in our patient.

OTHER CONSIDERATIONS

What if the patient had renal insufficiency or were on dialysis?

Sanderink et al assessed antifactor Xa levels and anti-Xa clearance in a study of healthy volunteers and patients with mild, moderate, or severe renal impairment given enoxaparin 40 mg once daily for 4 days.[32] On day 4, anti-Xa clearance was 39% lower in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) than in healthy controls (P = .0001), but anti-Xa exposure was not significantly different between controls and patients with mild or moderate renal impairment. The authors recommended a decrease in enoxaparin dosage to 30 mg/day in patients with creatinine clearance of 30 mL/min or less but no dosage adjustment in those with mild or moderate renal impairment, as reflected in enoxaparin labeling. In contrast, no adjustment in the dosage of dalteparin appears to be necessary in patients with severe renal insufficiency.[33]

In the case of dialysis patients, there are no studies to support using LMWH for pharmacologic prophylaxis. Because the risk of HIT is extremely low in patients on dialysis, especially compared with orthopedic surgery patients, expert consensus generally favors using UFH for VTE prophylaxis in patients on dialysis.

What if the patient weighed more than 100 kg?

Data are sparse in the obese medically ill population, but in a series of patients undergoing bariatric surgery, VTE prophylaxis with 40 mg of enoxaparin twice daily was associated with significant reductions in length of hospital stay, operating room time, and rates of postoperative VTE compared with 30 mg of enoxaparin twice daily, without any increase in bleeding complications.[34]

rate of major bleeding, although the incidence of major bleeding was low. The investigators concluded that the net clinical effect of extended-duration prophylaxis with enoxaparin is favorable, as only 46 patients would need to be treated to prevent one VTE event, whereas 224 patients would need to be treated to result in one major bleeding event.[21]

For this reason, it is reasonable to consider extended prophylaxis for hospitalized medical patients after identifying these patients' risk factors. In keeping with the trial's amended inclusion criteria, patients older than age 75 and those with cancer or prior VTE should receive special consideration for extended prophylaxis.

RECOMMENDED APPROACH TO VTE PREVENTION IN HOSPITALIZED MEDICAL PATIENTS

Given the wide gap between the evidence reviewed above and current practice worldwide,[8,22,23] we propose the algorithm presented in **Figure 2** for the prevention of VTE in hospitalized medical patients. Our recommended approach is guided by the principles below:

- All hospitalized medical patients should be

screened at the time of admission and patients at risk for VTE should receive prophylaxis.

- All patients with reduced mobility and one or more other risk factors for VTE are candidates for prophylaxis.
- Patients should be reassessed daily for the development of VTE risk factors during their hospitalization if risk factors are absent on admission.
- If screening or reassessment reveals any VTE risk factors, pharmacologic prophylaxis is the mainstay of therapy. If exclusion criteria for pharmacologic prophylaxis are present, mechanical prophylaxis with graduated compression stockings and intermittent compression devices should be used. For very high-risk medical patients without a contraindication to anticoagulants, combination prophylaxis with both an anticoagulant and mechanical devices is preferred.
- In this patient population, LMWH agents are preferred as pharmacologic prophylaxis over UFH and over fondaparinux (which is not currently approved by the US Food and Drug Administration for this population).
- If UFH is to be used in this patient population, 5,000 U *three times daily* is the preferred dosage.
- Extended pharmacologic prophylaxis should be considered in patients older than age 75 and in patients with a cancer diagnosis or a prior VTE episode.

DISCUSSION: ADDITIONAL PERSPECTIVES FROM THE AUTHORS

Dr. Jaffer: Dr. Spyropoulos, are there any guidelines, other than those from the ACCP, that speak to VTE prophylaxis in hospitalized medical patients? If so, what are their take-home messages and how do they differ from the ACCP guidelines?

Dr. Spyropoulos: I was part of the group that developed the International Consensus Statement (ICS) published in *International Angiology* in 2006,[11] which is more recent than the seventh ACCP guidelines, which were published in 2004. The ICS drew on much of the same data that the ACCP did, but we did an updated review of clinical trials.

For VTE prophylaxis in hospitalized medical patients, the ICS recommendations are more specific with regard to the type, dose, and dosing frequency of anticoagulant agents. First, they specify doses for both LMWH agents in this patient setting: 40 mg once daily for enoxaparin, and 5,000 IU once daily for dalteparin.

The ICS document also states that if UFH is the choice for prophylaxis, a regimen of 5,000 U three times daily should be considered. In the past year alone, two analyses suggest that three-times-daily dosing of UFH in medical patients provides superior efficacy to twice-daily dosing, although perhaps at the expense of more bleeding episodes.[12,16] It is important to remember that no large placebo-controlled trial supports the efficacy of a UFH regimen of 5,000 U twice daily in this population.

Finally, the ICS document states that fondaparinux 2.5 mg once daily is a viable option for prophylaxis in medical patients, based on the ARTEMIS trial,[3] even though this represents an off-label use.

Dr. Jaffer: Real-world use of VTE prophylaxis is far from optimal, especially in medical patients, and this is partly a result of system-of-care issues. I'd like to conclude by asking each of my colleagues to offer your perspectives on how your own institutions have improved their systems of care to promote better use of VTE prophylaxis and what lessons might be shared with others. Dr. McKean, you work at Brigham and Women's Hospital, which recently reported impressive results with an electronic alert system designed to increase clinicians' consideration of VTE risk assessment and use of prophylaxis.[24] Please tell us about that study and the alert system.

Dr. McKean: Despite many educational initiatives at Brigham and Women's Hospital, there were still some patients at high risk for VTE who were not receiving appropriate prophylaxis. What Dr. Samuel Goldhaber and his colleagues wanted to determine was whether changing the system of care could result in a reduced incidence of VTE.[24] They devised a computer software program linked to the patient database that used eight common risk factors to determine each hospitalized patient's risk profile for VTE. Each risk factor was weighted according to a point scale, with major risk factors (cancer, prior VTE, or hypercoagulability) assigned 3 points, the intermediate risk factor of surgery assigned 2 points, and minor risk factors (advanced age, obesity, immobility, or use of hormone replacement therapy or oral contraceptives) assigned 1 point. For patients with a total risk score of 4 or greater, the computer screen generates a color-coded VTE risk alert that requires the physician to acknowledge the alert and choose one of three options: order prophylaxis as appropriate, review a 60-page document on the computer to learn more about prophylaxis, or do nothing.

The study found that hospitalized patients who were randomized to treatment under the computer alert system were significantly more likely to receive VTE prophylaxis and significantly less likely to develop VTE than were patients randomized to a control group. The alert system reduced the risk of DVT or

PE at 90 days by 41% in patients considered to be at high risk. It was particularly interesting that the incidence of VTE was lower in the intervention group even when physicians chose not to use prophylaxis, which suggests that simply having this alert system in place improved outcomes, perhaps by raising awareness of the risk of VTE.[24]

Additional studies are needed to better understand physicians' behavior and determine why they seem to have a disproportionate fear of the risk of bleeding relative to the risk of clotting, including fatal PE, because that's really the heart of the matter. When patients are not given prophylaxis, often it's because of the fear of bleeding. It is not clear, however, why some of these patients did not receive mechanical devices as an alternative form of prophylaxis, but this seems to be the case worldwide, as shown recently by the multinational ENDORSE study.[22] Meanwhile, as we await studies to better understand physician perceptions and behaviors regarding prophylaxis, we need to work hard to change the system of care.

Dr. Deitelzweig: Over the past couple of years, the Ochsner Clinic has grown from a one-hospital teaching organization to a seven-hospital system with a mix of closed and open medical staff. The challenge is how to take a process that worked well in the one center, where appropriate prophylaxis was used about 90% of the time, and transfer it to the other centers in the larger system. We have endorsed several types of performance tools, such as the change-acceleration processes used by General Electric. The aim is to share a vision of heightening awareness. To do that, we've worked to mobilize the key stakeholders, at least half of them, to build algorithms that they all will endorse. It is easier said than done, however, and we've found it essential to involve both physicians and nonphysician colleagues from pharmacy and nursing who have political and organizational clout.

Dr. Brotman: At Johns Hopkins, I took a bit more draconian approach to this issue because I thought that hospitalists often knew that they should be using VTE prophylaxis but sometimes weren't, and I am not convinced that clinicians always look at prompts. So we came up with a system that incorporates both billing and documentation simultaneously. We put a hard stop on users' documentation so that they could not sign off on a note or bill for their care until they checked off the kind of VTE prophylaxis they were using. Since hospitalists ultimately care about billing for their work, this system has at least ensured that everybody has considered and documented VTE prophylaxis on a daily basis. There are other hard stops that can be implemented in computer order-entry systems as well, and we are considering ways to roll them out on a broader scale.

However, all of these systems can have problems because patient situations change from day to day. For instance, VTE prophylaxis is not necessarily indicated in a 38-year-old ambulatory patient who comes in with a sickle cell crisis, but you will need to reconsider if the patient ends up in acute chest syndrome in the intensive care unit. I don't yet have a good way to ensure that this is being done on a daily basis with all patients.

Dr. Amin: At the University of California, Irvine, we implemented an electronic alert system, but we locked users in so that they could not complete their admission orders until they answered questions about VTE prevention. This practice increased our VTE prophylaxis rates tremendously. Because we are a level I trauma center, we allow users to bypass the screens one time, but the next time they log in, even to get a simple lab result, they have to answer the questions about VTE prevention.

With any system you develop, you also have to continue with the education process, because clinicians sometimes get into bad habits or simply forget things.

Dr. Spyropolous: At Lovelace Medical Center, we didn't have the sophistication of an electronic order-entry system, but we had an experienced clinical pharmacist (the director of inpatient pharmacy) who helped to develop and champion VTE prevention guidelines that have then been used throughout the system in close conjunction with our hospitalists' rounds. This system has been used successfully for the past 7 years.

AUTHOR DISCLOSURES

Dr. Jaffer reported that he has received consulting fees and honoraria for teaching/speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim; he also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and the board of directors of the Anticoagulation Forum. **Dr. Amin** reported that he has received research funding and honoraria for speaking from Sanofi-Aventis, Eisai, and GlaxoSmithKline. **Dr. Brotman** reported that he has no financial relationships with commercial interests that are relevant to this article. **Drs. Deitelzweig and McKean** each reported that they have received honoraria for teaching/speaking from Sanofi-Aventis. **Dr. Spyropoulos** reported that he has received consulting fees from Sanofi-Aventis, Eisai, and Boehringer Ingelheim.

Each author received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the Cleveland Clinic Center for Continuing Education from the educational grant from Sanofi-Aventis underwriting this supplement. Sanofi-Aventis had no input on the content of the roundtable or this supplement.

REFERENCES

1. **Samama MM, Cohen AT, Darmon JY, et al.** A comparison of enoxaparin with placebo for the prevention of venous thrombo-

embolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999; 341:793–800.
2. **Leizorovicz A, Cohen AT, Turpie AG, et al.** Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation 2004; 110:874–879.
3. **Cohen AT, Davidson BL, Gallus AS, et al.** Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006; 332:325–329.
4. **Baglin TP, White K, Charles A.** Fatal pulmonary embolism in hospitalised medical patients. J Clin Pathol 1997; 50:609–610.
5. **Piazza G, Seddighzadeh A, Goldhaber SZ.** Double trouble for 2,609 hospitalized medical patients who developed deep vein thrombosis: prophylaxis omitted more often and pulmonary embolism more frequent. Chest 2007; 132:554–561.
6. **Amin A, Stemkowski S, Lin J, Yang G.** Thromboprophylaxis rates in US medical centers: success or failure? J Thromb Haemost 2007; 5:1610–1616.
7. **Geerts WH, Heit JA, Clagett GP, et al.** Prevention of venous thromboembolism. Chest 2001; 119(1 Suppl):132S–175S.
8. **Tapson VF, Decousus H, Pini M, et al.** Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest 2007; 132:936–945.
9. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):338S–400S.
10. **Dentali F, Douketis JD, Gianni M, Lim W, Crowther MA.** Meta-analysis: anticoagulant prophylaxis to prevent symptomatic venous thromboembolism in hospitalized medical patients. Ann Intern Med 2007; 146:278–288.
11. **Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; International Surgical Thrombosis Forum; International Union of Angiology; Union Internationale de Phlébologie.** Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). Int Angiol 2006; 25:101–161.
12. **Wein L, Wein S, Haas SJ, Shaw J, Krum H.** Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med 2007; 167:1476–1486.
13. **Mismetti P, Laporte-Simitsidis S, Tardy B, et al.** Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost 2000; 83:14–19.
14. **Lechler E, Schramm W, Flosbach CW.** The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. Haemostasis 1996; 26(Suppl 2):49–56.
15. **Kleber FX, Witt C, Vogel G, et al; the PRINCE Study Group.** Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J 2003; 145:614–621.
16. **King CS, Holley AB, Jackson JL, Shorr AF, Moores LK.** Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a meta-analysis. Chest 2007; 131:507–516.
17. **Burleigh E, Wang C, Foster D, et al.** Thromboprophylaxis in medically ill patients at risk for venous thromboembolism. Am J Health Syst Pharm 2006; 63(20 Suppl 6):S23–S29.
18. **Leykum L, Pugh J, Diuguid D, Papadopoulos K.** Cost utility of substituting enoxaparin for unfractionated heparin for prophylaxis of venous thrombosis in the hospitalized medical patient. J Hosp Med 2006; 1:168–176.
19. **Creekmore FM, Oderda GM, Pendleton RC, Brixner DI.** Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. Pharmacotherapy 2006; 26:1438–1445.
20. **Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ.** Venous thromboembolism in the outpatient setting. Arch Intern Med 2007; 167:1471–1475.
21. **Hull RD, Schellong SM Tapson VF, et al.** Extended-duration venous thromboembolism (VTE) prophylaxis in acutely ill medical patients with recent reduced mobility: the EXCLAIM study. Presentation at: International Society on Thrombosis and Haemostasis XXIst Congress; July 6–12, 2007; Geneva, Switzerland.
22. **Cohen AT, Tapson VF, Bergmann JF, et al.** Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008; 371:387–394.
23. **Kahn SR, Panju A, Geerts W, et al; CURVE study investigators.** Multicenter evaluation of the use of venous thromboembolism prophylaxis in acutely ill medical patients in Canada. Thromb Res 2007; 119:145–155.
24. **Kucher N, Koo S, Quiroz R, et al.** Electronic alerts to prevent thromboembolism among hospitalized patients. N Engl J Med 2005; 352:969–977.
25. **Anderson FA Jr, Wheeler HB, Goldberg RJ, et al.** A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991; 151:933–938.
26. **Howell MD, Geraci JM, Knowlton AA.** Congestive heart failure and outpatient risk of venous thromboembolism: a retrospective, case-control study. J Clin Epidemiol 2001; 54:810–816.
27. **Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P.** Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006; 367:1075–1079.
28. **Alikhan R, Cohen AT, Combe S, et al.** Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. Blood Coagul Firbinolysis 2003; 14:341–346.
29. **Anderson FA Jr, Spencer FA.** Risk factors for venous thromboembolism. Circulation 2003; 107(23 Suppl 1):I9–I16.
30. **Greinacher A, Warkentin TE.** Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. Thromb Res 2006; 118:165–176.
31. **Martel N, Lee J, Wells PS.** Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005; 106:2710–2715.
32. **Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX.** Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. Thromb Res 2002; 105:225–231.
33. **Douketis J, Cook D, Zytaruk N, et al.** Dalteparin thromboprophylaxis in critically ill patients with severe renal insufficiency: the DIRECT study [abstract]. J Thromb Haemost 2007; 5(Suppl 2): P-S-680.
34. **Scholten DJ, Hoedema RM, Scholten SE.** A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg 2002; 12:19–24.

Correspondence: *Amir K. Jaffer, MD, Chief, Division of Hospital Medicine, Leonard M. Miller School of Medicine, University of Miami, 1120 NW 14th Street, 933 CRB (C216), Miami, FL 33136; ajaffer@med.miami.edu.*

ALEX C. SPYROPOULOS, MD DANIEL J. BROTMAN, MD ALPESH N. AMIN, MD, MBA
STEVEN B. DEITELZWEIG, MD AMIR K. JAFFER, MD SYLVIA C. MCKEAN, MD

Prevention of venous thromboembolism in the cancer surgery patient

ABSTRACT

Cancer patients, especially those undergoing surgery for cancer, are at extremely high risk for developing venous thromboembolism (VTE), even with appropriate thromboprophylaxis. Anticoagulant prophylaxis in cancer surgery patients has reduced the incidence of VTE events by approximately one-half in placebo-controlled trials, and extended prophylaxis (for up to 1 month) has also significantly reduced out-of-hospital VTE events in clinical trials in this population. Clinical trials show no difference between low-molecular-weight heparin (LMWH) and unfractionated heparin in VTE prophylaxis efficacy or bleeding risk in this population, although the incidence of heparin-induced thrombocytopenia is lower with LMWH. The risk-benefit profile of low-dose anticoagulant prophylaxis appears to be favorable even in many cancer patients undergoing neurosurgery, for whom pharmacologic VTE prophylaxis has been controversial because of bleeding risks.

Venous thromboembolism (VTE) is a major complication of cancer, occurring in 4% to 20% of patients,[1] and is one of the leading causes of death in cancer patients, although these figures are believed to be underestimates, given the low autopsy rates among cancer patients.[2] In hospitalized cancer patients specifically, VTE is the second leading cause of death.[3,4] The risk of VTE in cancer patients undergoing surgery is three to five times greater than that in surgical patients without cancer.[4] Moreover, cancer patients with symptomatic deep vein thrombosis (DVT) exhibit a high risk of recurrent VTE that may persist for many years after the index event.[5]

VTE PREVENTION POSES PARTICULAR CHALLENGES IN CANCER PATIENTS

Until recently, data on VTE prevention specific to cancer patients have been sparse. Cancer patients have represented only a small subset (< 20%) of participants in most of the largest clinical trials of VTE prophylaxis. Until the past 2 or 3 years, clinicians largely have had to extrapolate their approach to VTE prophylaxis in cancer patients from data in patients without cancer, bearing in mind that cancer patients are among the populations at highest risk of developing VTE.

High rates of VTE, even with prophylaxis

What has been clear is that VTE prevention is a formidable challenge in this population, even when thromboprophylaxis is used. Despite thromboprophylaxis, cancer patients undergoing surgery have twice the risk of VTE and nonfatal pulmonary embolism (PE) and three times the risk of fatal PE compared with other surgical patients **(Table 1)**.[6,7]

Further insights have come from the @RISTOS project, a Web-based prospective registry of patients undergoing general, urologic, or gynecologic surgery for cancer at multiple centers in Italy.[8] Of the 2,372 patients tracked in this study, 82% received in-hospital VTE prophylaxis and 31% received prophylaxis following discharge. Despite this relatively high frequency of prophylaxis, however, the incidence of clinically overt VTE was 2.1% and the incidence of fatal VTE was 0.8%. Notably, most VTE events occurred after hospital discharge, and VTE was the most common cause of 30-day postoperative death in this registry.

RISK FACTORS: CANCER TYPE AND TREATMENT LOOM LARGE

Both the type and stage of a patient's cancer are important in assessing the risk of VTE. For men, cancers of the prostate, colon, brain, and lung have been associated with an increased risk of VTE. Among women, cancers of the breast, ovary, and lung have been especially implicated as risk factors for VTE.[9,10]

The type of cancer therapy also influences VTE risk:

- **Surgery.** Among patients who undergo cancer-related surgery, the rate of proximal DVT is 10% to 20%, the rate of clinically evident PE is 4% to 10%, and the incidence of fatal PE is 0.2% to 5%.[8,11]

See inside front cover for author affiliations. See end of article for author disclosures.

TABLE 1
Event rates in surgical patients with and without cancer who received anticoagulant prophylaxis*

	Noncancer surgery (n = 16,954)	Cancer surgery (n = 6,124)	*P* for difference
Postoperative VTE	0.61%	1.26%	< .0001
Nonfatal PE	0.27%	0.54%	< .0003
Autopsy-confirmed PE	0.11%	0.41%	.0001
Death	0.71%	3.14%	.0001

* In an international multicenter randomized trial using VTE prophylaxis with either unfractionated heparin or low-molecular-weight heparin.[6,7]

VTE = venous thromboembolism; PE = pulmonary embolism

• **Systemic treatments**, including chemotherapy and hormone therapy, are also associated with an increased risk of VTE.[12–15]

• **Central venous catheters.** Approximately 4% of cancer patients who have central venous catheters placed develop clinically relevant VTE.[16,17]

In addition to the above risks related to cancer treatments, the following have been identified as risk factors for VTE in surgical oncology patients:

• Age greater than 40 years (risk also increases steeply after age 60 and again after age 75)
• Cancer procoagulants
• Thrombophilia
• Length and complications of cancer surgery (ie, often involving tissue trauma and immobilization)
• Debilitation and slow recovery.

Another risk factor worth noting is perioperative transfusion, as illustrated in a recent study of 14,104 adults undergoing colorectal cancer resection.[18] The overall incidence of VTE in these patients was 1.0%, and the risk of death was nearly four times as great in patients who developed VTE as in those who did not. Notably, the need for transfusion was a marker of increased risk of VTE, particularly in women: women who received perioperative transfusions had almost double the risk of developing VTE compared with women who did not receive transfusions ($P = .004$).

CLINICAL TRIALS OF PROPHYLAXIS IN CANCER SURGERY PATIENTS

LMWH vs UFH for in-hospital prophylaxis

Two large randomized, double-blind trials have compared low-molecular-weight heparin (LMWH) with low-dose unfractionated heparin (UFH) for VTE prophylaxis in surgical cancer patients—the Enoxaparin and Cancer (ENOXACAN) study[19] and the Canadian Colorectal Surgery DVT Prophylaxis Trial.[20] Patients in these studies underwent surgery for abdominal or pelvic cancer (mostly colorectal cancer). Both studies compared 40 mg of the LMWH enoxaparin given once daily with 5,000 U of UFH given three times daily for 7 to 10 days postoperatively. Outcome measures were the presence of DVT determined by venography on day 7 to 10 and the incidence of symptomatic VTE. Rates of VTE were statistically equivalent between the two treatment arms in both ENOXACAN (14.7% with LMWH vs 18.2% with UFH) and the Canadian Colorectal Surgery study (9.4% with both therapies), as were rates of major bleeding (4.1% with LMWH vs 2.9% with UFH in ENOXACAN; 2.7% with LMWH vs 1.5% with UFH in the Canadian study).

These findings are consistent with a 2001 meta-analysis by Mismetti et al of all available randomized trials comparing LMWH with placebo or with UFH for VTE prophylaxis in general surgery.[21] This analysis found no differences in rates of asymptomatic DVT, clinical PE, clinical thromboembolism, death, major hemorrhage, total hemorrhage, wound hematoma, or need for transfusion between LMWH and UFH in patients undergoing either cancer-related surgery or surgery not related to cancer.

Fondaparinux for in-hospital prophylaxis

Subgroup analysis of the large randomized trial known as PEGASUS[22] sheds some light on the efficacy of the factor Xa inhibitor fondaparinux relative to LMWH for thromboprophylaxis in cancer surgery patients. PEGASUS compared fondaparinux 2.5 mg once daily with the LMWH dalteparin 5,000 IU once daily for 5 to 9 days in patients undergoing high-risk abdominal surgery. Among the study's 1,408 patients undergoing surgery for cancer, rates of VTE were 4.7% in the fondaparinux group compared with 7.7% in the LMWH group, a relative risk reduction of 38.6% with fondaparinux (95% CI, 6.7% to 59.6%). In contrast, in the rest of the PEGASUS population (patients undergoing abdominal surgery for reasons other than cancer), LMWH was nonsignificantly more efficacious at preventing VTE than was fondaparinux. Rates of major bleeding in this cancer subgroup were comparable between the two treatments.

Extended prophylaxis

Two additional randomized trials have evaluated extended prophylaxis with LMWH in surgical cancer patients—ENOXACAN II[23] and the Fragmin After Major Abdominal Surgery (FAME) study.[24]

In ENOXACAN II, patients undergoing surgery for abdominal or pelvic cancer first received 6 to 10 days of prophylaxis with enoxaparin 40 mg once daily and then were randomized in a double-blind fashion to an additional 21 days of enoxaparin or placebo.[23] Among 332 patients in the intent-to-treat analysis, the rate of VTE at the end of the double-blind phase was reduced from 12.0% with placebo to 4.8% with extended-duration enoxaparin (P = .02), an effect that was maintained at 3-month follow-up (P = .01). There was no significant difference between the two groups in rates of major bleeding events or any bleeding events.

In FAME, patients received 5,000 IU of dalteparin once daily for 1 week following major abdominal surgery and then were randomized in open-label fashion to either placebo or extended prophylaxis with dalteparin for 3 more weeks; a subanalysis examined outcomes in the 198 FAME participants whose abdominal surgery was for cancer.[24] Among these 198 cancer surgery patients, the rate of venography-documented VTE at 4 weeks was reduced from 19.6% with placebo to 8.8% with extended-duration dalteparin, a relative reduction of 55% (P = .03). The rate of proximal DVT was reduced from 10.4% to 2.2% with extended prophylaxis, a relative reduction of 79% (P = .02).

The number needed to treat with extended LMWH prophylaxis to prevent one VTE event was 14 in ENOXACAN II[23] and 9 in the FAME subanalysis of cancer surgery patients.[24]

New systematic review of relevant trials

Leonardi et al recently published a systematic review of 26 randomized controlled trials of DVT prophylaxis in 7,639 cancer surgery patients.[25] They found the overall incidence of DVT to be 12.7% in those who received pharmacologic prophylaxis compared with 35.2% in controls. They also found high-dose LMWH therapy (> 3,400 U daily) to be associated with a significantly lower incidence of DVT than low-dose LMWH therapy (≤ 3,400 U daily) (7.9% vs 14.5%, respectively; P < .01). No differences were demonstrated between LMWH and UFH in preventing DVT, DVT location, or bleeding. Bleeding complications requiring discontinuation of pharmacologic prophylaxis occurred in 3% of patients overall.

Implications of HIT

The sequelae of heparin-induced thrombocytopenia (HIT) can have major consequences for cancer surgery patients. The incidence of HIT is markedly lower with LMWH than with UFH, as demonstrated in a nested case-control study by Creekmore et al.[26] These researchers also found that the average cost of an admission during which HIT developed was nearly four times as great as the average cost of an admission during which UFH or LMWH was given without development of HIT ($56,364 vs $15,231; P < .001).

EVIDENCE IN SPECIFIC ONCOLOGIC POPULATIONS

Most of the patients in the trials reviewed above underwent abdominal surgery for malignancy. Although studies of VTE prophylaxis in patients undergoing nonabdominal cancer surgery are relatively few, some data are available for a few other specific oncologic populations, as reviewed below.

Surgery for gynecologic cancer

There is a paucity of randomized controlled trials or prospective observational studies on VTE and its prevention in the gynecologic cancer surgery population. Based on small historical studies, the postoperative risk of VTE in this population varies from 12% to 35%.[27,28] Twice-daily administration of UFH 5,000 U appears to be ineffective as VTE prophylaxis in this population, but increasing the frequency to three times daily reduces VTE risk by 50% to 60% compared with placebo. Once-daily LMWH is comparable to three-times-daily UFH in efficacy and safety in this population.

A systematic Cochrane review of eight randomized controlled trials in patients undergoing major gynecologic surgery revealed that heparin prophylaxis (either UFH or LMWH) reduces the risk of DVT by 70% compared with no prophylaxis, with an identical risk reduction specifically among women with malignancy (odds ratio, 0.30; 95% CI, 0.10 to 0.89).[29] This review found no evidence that anticoagulation reduces the risk of PE following major gynecologic surgery. LMWH and UFH were similar in efficacy for preventing DVT and had a comparable risk of bleeding complications.

Surgery for urologic cancer

The risk of VTE and the benefits of thromboprophylaxis also are poorly studied in patients undergoing surgery for urologic cancer.

The risk of VTE varies with the type of urologic surgery and the method used to diagnose VTE. For instance, patients undergoing radical retropubic prostatectomy have been reported to develop DVT at rates of 1% to 3%, PE at rates of 1% to 3%, and fatal PE at a rate of 0.6%, whereas the incidences of these events are somewhat higher in patients undergoing cystectomy: 8% for DVT, 2% to 4% for PE, and 2% for fatal PE. Radiologic diagnosis of thromboembolism in pelvic surgery patients has yielded higher incidences, with DVT rates of 21% to 51% and PE rates of 11% to 22%.[30]

Small studies suggest that prophylaxis with either

TABLE 2
Pooled outcomes of three randomized controlled trials of LMWH prophylaxis in neurosurgery patients*

Event	Control†	LMWH	RR‡	NNT/ NNH§	*P* for difference
VTE	28.3%	17.5%	0.6	9	< .001
Proximal DVT	12.5%	6.2%	0.5	16	< .01
Any bleeding	3.0%	6.1%	2.0	33	.02
Major bleeding	1.3%	2.2%	1.7	115	.30

* Adapted from data in the meta-analysis of Iorio and Agnelli.[33]

† Control was placebo with or without graduated compression stockings (GCS); in the two studies in which control patients wore GCS, patients in the LMWH group also wore GCS.

‡ Relative risk with LMWH vs control.

§ Across the three pooled trials, 1 major nonfatal bleeding event was observed for every 7 proximal DVTs prevented.

LMWH = low-molecular-weight heparin; RR = relative risk; NNT/NNH = number needed to treat/harm; VTE = venous thromboembolism; DVT = deep vein thrombosis

low-dose UFH or LMWH is both effective in reducing VTE risk and safe in urologic cancer surgery patients, although pharmacologic prophylaxis poses a possible increased risk of pelvic hematoma and lymphocele formation in this population.[30]

Neurosurgery

Most neurosurgical procedures are performed for malignancies. The risk of venographic VTE in patients undergoing neurosurgery is approximately 30% to 40%.[31,32] Likewise, the risks of intracranial or intraspinal hemorrhage in these patients are high. For this reason, mechanical methods of VTE prophylaxis are preferred in these patients. The use of anticoagulant prophylaxis remains controversial in this setting, although more recent data suggest that it might be safer than previously recognized.

A meta-analysis of studies of pharmacologic prophylaxis of VTE in neurosurgery included three randomized controlled trials that compared LMWH, with or without mechanical prophylaxis, to placebo plus mechanical prophylaxis or placebo alone in a total of 922 neurosurgery patients.[33] As detailed in **Table 2**, the analysis demonstrated statistically significant reductions in the risks of VTE and proximal DVT in favor of LMWH, with a statistically significant doubling in the risk of any bleeding and a nonsignificant 70% increase in the risk of major bleeding with LMWH therapy. The number needed to treat to prevent 1 proximal DVT was 16, while the number needed to treat to cause 1 major bleeding event was 115. A risk-benefit analysis showed that the use of LMWH in neurosurgery patients was associated with 1 major nonfatal bleeding event for every 7 proximal DVTs prevented. When a fourth randomized trial was included in the analysis, comparing UFH 5,000 U three times daily with no prophylaxis, rates of VTE and bleeding events remained similar to those for the LMWH trials alone.

GUIDELINES FOR VTE PROPHYLAXIS IN THE CANCER SURGERY PATIENT

American College of Chest Physicians

The American College of Chest Physicians' Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy makes a number of recommendations regarding VTE prevention in patients undergoing surgery for cancer, as outlined in **Table 3**.[34]

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) recently published clinical practice guidelines on venous thromboembolic disease in cancer patients.[35] The defined at-risk population for these guidelines is the adult cancer inpatient with a diagnosis of (or clinical suspicion for) cancer. The guidelines recommend prophylactic anticoagulation (category 1 recommendation) with or without a sequential compression device as initial prophylaxis, unless the patient has a relative contraindication to anticoagulation, in which case mechanical prophylaxis (sequential compression device or graduated compression stockings) is recommended. (A category 1 recommendation indicates "uniform NCCN consensus, based on high-level evidence.")

The NCCN guidelines include a specific recommended risk-factor assessment, which includes noting the patient's age (VTE risk increases beginning at age 40 and then steeply again at age 75), any prior VTE, the presence of familial thrombophilia or active cancer, the use of medications associated with increased VTE risk (chemotherapy, exogenous estrogen compounds, and thalidomide or lenalidomide), and a number of other risk factors for VTE as outlined in the prior two articles in this supplement. The NCCN guidelines explicitly call for assessment of modifiable risk factors for VTE (ie, smoking or other tobacco use, obesity, and a low level of activity or lack of exercise) and call for active patient education on these factors.

American Society of Clinical Oncology

The American Society of Clinical Oncology (ASCO) recently released guidelines on VTE prevention and treatment in patients with cancer;[1] their key recom-

TABLE 3
American College of Chest Physicians recommendations for thromboprophylaxis in patients with cancer and/or undergoing cancer surgery[34]

Cancer patients undergoing surgical procedures should receive prophylaxis that is appropriate for their current risk state **(Grade 1A*)**

In cancer patients undergoing general, gynecologic, or urologic surgery:

- Prophylaxis with low-dose UFH 5,000 U three times daily or with LMWH > 3,400 U daily† is recommended **(Grade 1A* for both UFH and LMWH)**
- Mechanical prophylaxis with graduated compression stockings and/or an intermittent pneumatic compression device is recommended for use in combination with pharmacologic prophylaxis **(Grade 1C+*)**

In patients who have undergone major cancer surgery, postdischarge prophylaxis with LMWH is recommended **(Grade 2A*)**

In cancer patients, routine prophylaxis is *not* recommended to prevent thrombosis related to long-term indwelling central venous catheters; specifically, clinicians should not use LMWH **(Grade 2B*)** or fixed-dosed warfarin **(Grade 1B*)** in this setting

* Key to recommendation grades:
1A Based on RCTs without important limitations. Strong recommendation; can apply to most patients in most circumstances without reservation.
1C+ No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies. Strong recommendation; can apply to most patients in most circumstances.
1B Based on RCTs with important limitations. Strong recommendation; likely to apply to most patients.
2A Based on RCTs without important limitations. Intermediate-strength recommendation; best action may differ depending on circumstances or patient or societal values.
2B Based on RCTs with important limitations. Weak recommendation; alternate approaches likely to be better for some patients under some circumstances.

† Translates to 5,000 IU daily for dalteparin and 40 mg daily for enoxaparin.

UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; RCTs = randomized controlled trials

TABLE 4
American Society of Clinical Oncology recommendations for VTE prevention in patients with cancer[1]

Hospitalized patients with cancer should be considered candidates for VTE prophylaxis with UFH, LMWH, or fondaparinux in the absence of bleeding or other contraindications to anticoagulation.

All patients undergoing major surgery for malignant disease should be considered for thromboprophylaxis with low-dose UFH, LMWH, or fondaparinux starting as early as possible for at least 7–10 days, unless contraindicated. Mechanical methods may be added to anticoagulation in very high-risk patients but should not be used alone unless anticoagulation is contraindicated. LMWH for up to 4 weeks may be considered after major abdominal/pelvic surgery with residual malignant disease, obesity, and a previous history of VTE.

Ambulatory patients with cancer receiving systemic chemotherapy do not require routine pharmacologic prophylaxis unless they are receiving thalidomide or lenalidomide, owing to these agents' thrombotic risk.

VTE = venous thromboembolism; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin

mendations for prevention are summarized in **Table 4**. Notable differences from the recommendations of the Seventh ACCP Conference are the ASCO guidelines' inclusion of fondaparinux among recommended prophylactic options for this population and more explicit recommendations on the prophylactic use of LMWH. Also, for treatment of cancer patients with *established* VTE, ASCO specifies that LMWH is the preferred anticoagulant for both initial and continuing treatment.

Our recommended algorithm

Drawing from the above formal society guidelines and the published literature, we recommend the algorithm in **Figure 1** as a practical approach to VTE prevention in patients undergoing major surgery for cancer.

LINGERING CHALLENGE OF UNDERUTILIZATION

Despite this consensus on ways to reduce thromboembolic risk in this population and the clear evidence of the benefit of VTE prophylaxis in patients with cancer, data from several registries confirm a persistently low utilization of prophylaxis in patients with cancer.[36–38] The global Fundamental Research in Oncology and Thrombosis (FRONTLINE) study surveyed 3,891 clinicians who treat cancer patients regarding their practices with respect to VTE in those patients.[36] The survey found that only 52% of respondents routinely used thromboprophylaxis for their surgical patients with cancer. More striking, however, was the finding that most respondents routinely considered thromboprophylaxis in only 5% of their medical oncology patients. These data are echoed by findings of other retrospective medical record reviews in patients undergoing major abdominal or abdominothoracic surgery (in many cases for cancer), with VTE prophylaxis rates ranging from 38% to 75%.[37,38]

SUMMARY

Patients undergoing surgery for cancer have an increased risk of VTE and fatal PE, even when thromboprophylaxis is used. Nevertheless, prophylaxis with either LMWH or UFH does reduce venographic VTE event rates in these patients. If UFH is chosen for prophylaxis, a three-times-daily regimen should be used

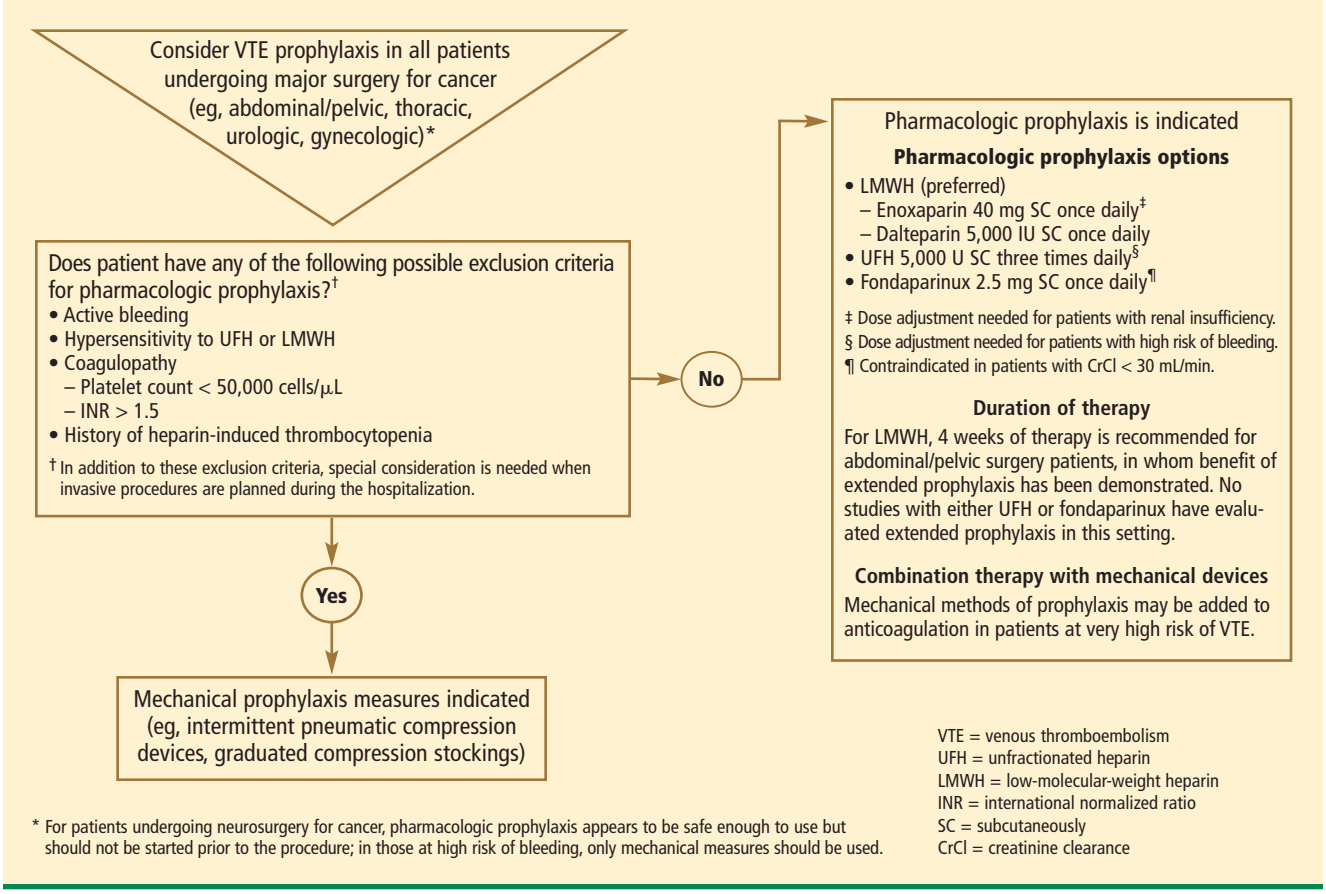


FIGURE 1. Algorithm for VTE prophylaxis in the patient undergoing major surgery for cancer.

in this population. In specific surgical cancer populations, especially those undergoing abdominal surgery, out-of-hospital prophylaxis with once-daily LMWH is warranted. Current registries reveal that compliance with established guidelines for VTE prophylaxis in this population is low.

DISCUSSION: ADDITIONAL PERSPECTIVES FROM THE AUTHORS

Dr. Jaffer: Dr. Amin, based on your study on thromboprophylaxis rates in US medical centers, will you comment on rates of prophylaxis for cancer surgery patients?

Dr. Amin: The overall study included approximately 200,000 medical patients and about 80,000 surgical patients enrolled over more than a 3-year period between 2002 and 2005.[39,40] Our goal was to assess rates of prophylaxis and, when it was provided, whether it was appropriate (in terms of type, dosage, and duration) based on the ACCP guidelines. A subanalysis assessed medical cancer patients and surgical cancer patients separately. Medical cancer patients received thromboprophylaxis 56% of the time but received *appropriate* prophylaxis only 28% of the time. Among surgical cancer patients, appropriate prophylaxis was given only about 24% of the time for those undergoing gynecologic surgery and about 12% of the time for those undergoing neurosurgery. These percentages are consistent with data from other national registries, such as the IMPROVE registry, which documented prophylaxis rates on the order of 45% in medical patients with cancer.[41] We also analyzed the data according to individual practitioners and found that medical oncologists use prophylaxis about 25% of the time, which is relatively consistent with other providers, such as internists and surgeons.

So there is a huge opportunity to improve rates of prophylaxis for this group of patients that national guidelines say are at high risk. Why is prophylaxis so underutilized in the cancer population? One factor may be a misperception about the risk of bleeding with anticoagulants. Yet several studies have shown that the rate of bleeding from prophylaxis is extremely low, whether LWMH or UFH is used, so more aware-

ness of actual bleeding risk is needed. Another factor is the obvious focus among internists and oncologists on *treating* the patient, with perhaps a reduced consideration of prophylaxis and prevention. A third factor may be a concern about thrombocytopenia. However, in our study of prophylaxis rates in US medical centers, we excluded patients who had thrombocytopenia, yet rates of prophylaxis were still low. Nothing in the literature indicates that anticoagulants cannot be used in patients with platelet counts of 50,000 to 150,000 cells/μL or higher, so this suggests that we need to do more education.

Dr. Jaffer: Dr. Brotman, can you tell us more about how clinicians in practice should use prophylaxis in their neurosurgery patients, such as those undergoing craniotomy or spine surgery for cancer? What is the safest and most efficacious way to prevent DVT in these patients?

Dr. Brotman: First, it's important to recognize that some sort of prophylaxis needs to be used. Neurosurgery patients are at an extremely high risk for thromboembolic events, and such events are often fatal in these patients. Having said that, the jury is still out on whether the prophylaxis in these patients should be compression devices or anticoagulation. This gives physicians some latitude in their decisions. They can decide not to use pharmacologic prophylaxis so long as they use pneumatic compression devices consistently, perhaps even starting during the operation and certainly throughout hospitalization when the patient is immobilized.

Certainly, the concerns about using full-dose anticoagulation in the immediate postoperative setting in neurosurgery patients are valid. Yet these patients are at very high risk for thromboembolic events, and if we take too cautious an approach to prophylaxis in the immediate perioperative setting, more patients are going to have thromboembolic events, at which point management decisions become much more difficult. The risk of intracranial bleeding with anticoagulation to treat a patient who develops a DVT at postoperative day 10 will certainly be higher than it would have been with lower-dose perioperative prophylactic anticoagulation. Plus, if you put in a filter at that point, the outcomes tend to be poor. Therefore, I believe there is some degree of risk that we should be willing to take with regard to perioperative bleeding, even in neurosurgery patients.

Dr. McKean: I'd like to make a point about combination prophylaxis. At many institutions, compression stockings and sequential compression devices are used preoperatively and intraoperatively, and then pharmacologic prophylaxis—for example, twice-daily UFH—is used postoperatively. There is concern that these patients are hypercoagulable, and most clinicians believe that mechanical prophylaxis alone, even with sequential compression devices plus compression stockings, is not aggressive enough in these high-risk patients.

Dr. Jaffer: Dr. Spyropoulos, what is the optimal duration of pharmacologic prophylaxis for cancer surgery patients?

Dr. Spyropoulos: First let's consider in-hospital prophylaxis. The supportive data for in-hospital prophylaxis are strong, and the duration of therapy used in the major in-hospital prophylaxis trials was 7 to 10 days. With regard to extended prophylaxis, we have at least two moderately sized randomized controlled trials, ENOXACAN II[23] and the substudy of FAME,[24] that demonstrated that extending prophylaxis with LMWH at doses of 3,400 U once daily (5,000 IU of dalteparin; 40 mg of enoxaparin) reduces VTE risk at postoperative day 30. Also, recent data from the @RISTOS registry show that in cancer surgery patients, especially those having abdominal or pelvic procedures, the leading cause of 30-day mortality was VTE.[8] This registry also shows that despite prophylaxis, the rate of symptomatic VTE can be as high as 2%, with the rate of fatal VTE approaching 1%. Thus, in cancer patients undergoing abdominal or pelvic surgery, physicians should strongly consider prophylaxis of up to 30 days' duration.

Dr. Jaffer: One striking finding from the @RISTOS registry was that 40% of VTE events in these cancer surgery patients occurred after postoperative day 21. This really underscores the need to consider prophylaxis for at least 4 weeks in these patients in real-world practice.

Dr. Brotman: The other striking finding from that registry was that the in-hospital prophylaxis rate was quite high, about 80%, and the rate of extended prophylaxis approached 35%. These are rates that are rarely achieved in clinical practice. Yet despite these high levels of prophylaxis, patients in this registry still had a high incidence of morbidity and mortality from VTE. This suggests that we need to improve our out-of-hospital VTE prevention paradigms.

Dr. Jaffer: Dr. Deitelzweig, oncologists and internists are often unsure about whether their ambulatory cancer patients who are receiving chemotherapy should be on any form of prophylaxis. What is your opinion?

Dr. Deitelzweig: That question comes up regularly because these patients are encountered across many medical specialties. At this point, all of the large organizations, including ASCO and NCCN, are advocating that prophylaxis is not indicated for such patients.

Case studies in cancer surgery patients

CASE 1: SURGERY FOR OVARIAN CANCER

A 54-year-old woman is undergoing debulking surgery for ovarian adenocarcinoma. Her only comorbid condition is well-controlled hypertension, and she has no history of VTE. Her body mass index is 32.

True or false? *Pharmacologic prophylaxis with low-dose UFH has been proven superior to mechanical prophylaxis for the prevention of VTE in this setting.*

Strictly speaking, this is false, but that is not the end of the story. Not every specific patient population has been studied with adequate statistical power, so in some cases extrapolation from other patient populations is justified. This woman is at high risk for VTE despite her young age and not having a prior VTE. Her risk factors for VTE are obesity, an advanced malignancy (as evidenced by the need for a debulking procedure), and the risk of a hypercoagulable state from her adenocarcinoma.

In the ACCP guidelines,[34] intermittent pneumatic compression devices are considered acceptable prophylaxis in the setting of our case patient. This contrasts with other patients undergoing high-risk surgical procedures, such as orthopedic surgery patients.

The data to support this recommendation are sparse, however. There is one randomized trial that directly compared pneumatic compression devices with low-dose UFH.[42] Each arm of the study contained about 100 patients, and there were more thrombi in the low-dose UFH arm than in the pneumatic compression arm (7 vs 4, respectively), but this difference was not statistically significant, as there was only a handful of events. Low-dose UFH also was associated with higher rates of blood transfusion and increased volumes of retroperitoneal drainage, raising some concern over safety, but these complications did not lead to an increase in subsequent operations to decompress hematomas.

Although this study's sample size was inadequate for drawing conclusions, many gynecologic surgeons are relying on mechanical prophylaxis as a result of these data, citing concern that pharmacologic prophylaxis has not specifically been proven superior to pneumatic compression devices in these patients. We would caution, however, that absence of proof is not proof of absence. When examining a data set this small in the face of an abundance of data in other cancer surgeries and other types of surgeries indicating that LMWH and UFH work very well in the prevention of VTE—and in some cases work better than pneumatic compression—perhaps we should not restrict ourselves to this single study to guide our decision-making.

True or false? *In studies demonstrating efficacy of LMWH and/or UFH for prevention of perioperative VTE in patients undergoing abdominal pelvic surgery for malignancy, therapy has generally been started preoperatively rather than postoperatively.*

This is true. In all major trials examining pharmacologic prophylaxis in patients undergoing abdominal pelvic surgery for malignancy, treatment was initiated preoperatively, often 2 hours before surgery.[43] This has also been the general timing of administration of anticoagulation in the general surgery population.

Nevertheless, clinical practice often differs from practices demonstrated in the literature to be effective. Data from randomized trials tell us that preoperative administration of LMWH and UFH, when used in prophylactic doses, is efficacious and adequately safe, yet reluctance to perform invasive procedures persists in patients who have received prophylactic doses of anticoagulation preoperatively.

True or false? *Mechanical measures for prophylaxis are widely used in patients like this, but no randomized trials have demonstrated their efficacy.*

This is false, but again the answer is compromised by the small sample size of relevant trials. One small study (N = 107) has documented the efficacy of sequential compression devices for 5 days in patients undergoing gynecologic cancer surgery.[44] In this study, 13% of patients who received the compression devices developed VTE compared with 35% of controls. Although this was a small study, the extremely high incidence of VTE in patients undergoing gynecologic cancer surgery is concerning. Even though these patients are not always elderly, they represent a very high-risk population that warrants prophylaxis as aggressive as what we use in our orthopedic surgery patients.

What should be recommended as perioperative prophylaxis in this patient?

Pharmacologic prophylaxis is the best-studied approach, and we would encourage its use in this case even though evidence from large randomized prospective trials in this specific population is lacking.

AUTHOR DISCLOSURES

Dr. Spyropoulos reported that he has received consulting fees from Sanofi-Aventis, Eisai, and Boehringer Ingelheim. **Dr. Brotman** reported that he has no financial relationships with commercial interests that are relevant to this article. **Dr. Amin** reported that he has received research funding and honoraria for speaking from Sanofi-Aventis, Eisai, and GlaxoSmithKline. **Drs. Deitelzweig and McKean** each reported that they have received honoraria for teaching/speaking from Sanofi-Aventis. **Dr. Jaffer** reported that he has received consulting fees and honoraria for teaching/speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim; he also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and the board of directors of the Anticoagulation Forum.

Each author received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the Cleveland Clinic Center for Continuing Education from the educational grant from Sanofi-Aventis underwriting this supplement. Sanofi-Aventis had no input on the content of the roundtable or this supplement.

CASE 2: SURGERY FOR GLIOBLASTOMA

A 43-year-old previously healthy man undergoes neuroimaging following a seizure and is found to have a large heterogeneous brain tumor invading the corpus callosum. Resection is planned.

True or false? *Prophylactic anticoagulation should be discouraged based on the risk of perioperative hemorrhage.*

This is false, but with a caveat. The consequences of an intracranial hemorrhage are often catastrophic. Despite this, researchers have studied systematically the use of pharmacologic prophylaxis in patients undergoing neurosurgery. In most of these studies, the anticoagulation was initiated the day after surgery rather than prior to surgery, in contrast to studies in patients undergoing abdominal pelvic surgery.

Agnelli et al conducted a study of 307 neurosurgical patients randomized to compression stockings alone or compression stockings plus enoxaparin.[31] Ninety-seven percent of patients underwent surgery for a tumor, and the procedure was intracranial in 85%. Enoxaparin 40 mg subcutaneously once daily (or matching placebo) was started the day after surgery.

Enoxaparin was associated with a 49% relative reduction ($P = .004$) in the incidence of VTE. Intracranial bleeding occurred in 4 placebo recipients and 3 enoxaparin recipients, illustrating that neurosurgery patients are at risk for intracranial hemorrhage but that prophylactic doses of anticoagulation are probably not the primary driver; instead, the surgery itself may be the main cause of hemorrhaging. There was a trend toward an increase in minor but not major bleeding with enoxaparin. Sixty-day mortality was no different between the groups, although 2 patients randomized to placebo died of autopsy-proven PE.[31]

Neurosurgery patients are at high risk for fatal thromboembolic disease, and even though intracranial hemorrhage is probably the most feared complication, it is not certain to cause death more often than VTE does. In this study, more patients died from fatal PE than from anticoagulation-associated intracranial hemorrhage, although the difference was not statistically significant.[31]

A meta-analysis examining the use of LMWH or UFH prophylaxis in neurosurgery patients found a 52% relative reduction in both proximal thromboembolic events and silent distal events with anticoagulant prophylaxis.[33] The number needed to treat to prevent one proximal VTE was 16, underscoring these patients' high risk of thrombosis. Among 1,022 patients evaluated for safety, adjudicated bleeding deaths occurred in 2 controls and 2 treated patients. Among the treated patients, one hemorrhage started during surgery, prior to anticoagulant use, and the other occurred during full-dose anticoagulation and after confirmed VTE, which again suggests that intracranial bleeding may be more feared than real for most patients. Among the 827 patients evaluated for efficacy, fatal thromboembolic events occurred in 1 treated patient and 2 controls. Anticoagulant prophylaxis was associated with a statistically significant increase in minor bleeding but not major bleeding.

The surgeon agrees to use pharmacologic prophylaxis and also decides to use sequential compression devices. The surgery is successful, but on postoperative day 22 the patient presents from rehabilitation with swelling of the left leg. Ultrasonography confirms an acute left common femoral DVT.

True or false? *Given the risk of full-dose anticoagulation in this patient, an inferior vena cava (IVC) filter should be placed.*

This is false. Placement of an IVC filter is not recommended in this patient unless reoperation is anticipated, the patient already has had surgical bleeding complications, or the patient is at uniquely high bleeding risk for some other reason.

A study from the 1980s illustrates a favorable overall risk-benefit profile for anticoagulation in glioma surgery.[45] The study assessed postoperative treatment of documented VTE (not merely VTE prophylaxis) in 109 patients with glioma, 103 of whom were treated with anticoagulants. Of the 6 patients who were not treated with anticoagulants, 3 suffered a fatal PE. Among the 103 patients who received treatment with full-dose anticoagulation, 3 suffered intracranial hemorrhage. Thus, although full-dose anticoagulation did increase the risk of bleeding in neurosurgery patients with documented VTE, this risk clearly did not outweigh the benefit of treating VTE, as demonstrated by the 50% rate of fatal PE in the absence of treatment.

IVC filters are often used in patients who have had recent neurosurgery because these patients are believed to be at increased risk of intracranial hemorrhage with anticoagulation. Levin et al examined 42 cases in which an IVC filter was placed in patients with central nervous system tumors.[46] Despite the IVC filter, 12% of patients developed PE and 57% developed either IVC or filter thrombosis, recurrent DVT, or post-phlebitic syndrome. The authors concluded that the complication rate associated with an IVC filter in this population is higher than perceived and outweighs the risk of anticoagulation.

REFERENCES

1. **Lyman GH, Khorana AA, Falanga A, et al.** American Society of Clinical Oncology Guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007; 25:5490–5505.
2. **Khorana AA, Francis CW, Culakova E, et al.** Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007; 5:632–634.
3. **Ambrus JL, Ambrus CM, Mink IB, Pickren JW.** Causes of death in cancer patients. J Med 1975; 6:61–64.
4. **Donati MB.** Cancer and thrombosis. Haemostasis 1994; 24:128–131.
5. **Prandoni P, Lensing AW, Cogo A, et al.** The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125:1–7.
6. **Haas S, Wolf H, Kakkar AK, Fareed J, Encke A.** Prevention of fatal pulmonary embolism and mortality in surgical patients: a randomized double-blind comparison of LMWH with unfractionated heparin. Thromb Haemost 2005; 94:814–819.
7. **Kakkar AK, Haas S, Wolf H, Encke A.** Evaluation of perioperative fatal pulmonary embolism and death in cancer surgical patients: the MC-4 cancer substudy. Thromb Haemost 2005; 94:867–871.
8. **Agnelli G, Bolis G, Capussotti L, et al.** A clinical outcome-based

prospective study on venous thromboembolism after cancer surgery: the @RISTOS project. Ann Surg 2006; 243:89–95.
9. **Levitan N, Dowlati A, Remick SC, et al.** Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy: risk analysis using Medicare claims data. Medicine (Baltimore) 1999; 78:285–291.
10. **Levine M, Gent M, Hirsh J, et al.** A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334:677–681.
11. **Bergqvist D.** Risk of venous thromboembolism in patients undergoing cancer surgery and options for thromboprophylaxis. J Surg Oncol 2007; 95:167–174.
12. **Heit JA, Silverstein MD, Mohr DN, et al.** Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000; 160:809–815.
13. **Sallah S, Wan JY, Nguyen NP.** Venous thrombosis in patients with solid tumors: determination of frequency and characteristics. Thromb Haemost 2002; 87:575–579.
14. **Kröger K, Weiland D, Ose C, et al.** Risk factors for venous thromboembolic events in cancer patients. Ann Oncol 2006; 17:297–303.
15. **Blom JW, Vanderschoot JP, Oostindiër MJ, et al.** Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: results of a record linkage study. J Thromb Haemost 2006; 4:529–535.
16. **Couban S, Simpson DR, Barnett MJ, et al.** A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood 2002; 100:1525–1531.
17. **Walshe LJ, Malak SF, Eagan J, Sepkowitz KA.** Complication rates among cancer patients with peripherally inserted central catheters. J Clin Oncol 2002; 20:3276–3281.
18. **Nilsson KR, Berenholtz SM, Garrett-Mayer E, et al.** Association between venous thromboembolism and perioperative allogeneic transfusion. Arch Surg 2007; 142:126–133.
19. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. Br J Surg 1997; 84:1099–1103.
20. **McLeod RS, Geerts WH, Sniderman KW, et al.** Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian Colorectal DVT Prophylaxis Trial: a randomized, double-blind trial. Ann Surg 2001; 233:438–444.
21. **Mismetti P, Laporte S, Darmon JY, Buchmüller A, Decousus H.** Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001; 88:913–930.
22. **Agnelli G, Bergqvist D, Cohen AT, et al, on behalf of the PEGASUS investigators.** Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg 2005; 92:1212–1220.
23. **Bergqvist D, Agnelli G, Cohen AT, et al.** Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346:975–980.
24. **Rasmussen MS, Wille-Jorgensen P, Jorgensen LN, et al.** Prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) following major abdominal surgery for malignancy [abstract 186]. Blood 2003; 102:56a.
25. **Leonardi MJ, McGory ML, Ko CY.** A systematic review of deep venous thrombosis prophylaxis in cancer patients: implications for improving quality. Ann Surg Oncol 2007; 14:929–936.
26. **Creekmore FM, Oderda GM, Pendleton RC, Brixner DI.** Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. Pharmacotherapy 2006; 26:1438–1445.
27. **Walsh JJ, Bonnar J, Wright FW.** A study of pulmonary embolism and deep leg vein thrombosis after major gynaecological surgery using labeled fibrinogen-phlebography and lung scanning. J Obstet Gynaecol Br Commonw 1974; 81:311–316.
28. **Clarke-Pearson DL, Synan IS, Colemen RE, et al.** The natural history of postoperative venous thromboemboli in gynecologic oncology: a prospective study of 382 patients. Am J Obstet Gynecol 1984; 148:1051–1054.
29. **Oates-Whitehead RM, D'Angelo A, Mol B.** Anticoagulant and aspirin prophylaxis for preventing thromboembolism after major gynaecological surgery. Cochrane Database Syst Rev 2003; (4):CD003679.
30. **Kibel AS, Loughlin KR.** Pathogenesis and prophylaxis of postoperative thromboembolic disease in urological pelvic surgery. J Urol 1995; 153:1763–1774.
31. **Agnelli G, Piovella F, Buoncristiani P, et al.** Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med 1998; 339:80–85.
32. **Semrad TJ, O'Donnell R, Wun T, et al.** Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg 2007; 106:601–608.
33. **Iorio A, Agnelli G.** Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. Arch Intern Med 2000; 160:2327–2332.
34. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):338S–400S.
35. **National Comprehensive Cancer Network.** NCCN Clinical Practice Guidelines in Oncology. Venous thromboembolic disease. V.1.2007. http://www.nccn.org/professionals/physician_gls/PDF/vte.pdf. Accessed December 5, 2007.
36. **Kakkar AK, Levine M, Pinedo HM, Wolff R, Wong J.** Venous thrombosis in cancer patients: insights from the FRONTLINE survey. Oncologist 2003; 8:381–388.
37. **Stratton MA, Anderson FA, Bussey HI, et al.** Prevention of venous thromboembolism: adherence to the 1995 American College of Chest Physicians consensus guidelines for surgical patients. Arch Intern Med 2000; 160:334–340.
38. **Bratzler DW, Raskob GE, Murray CK, Bumpus LJ, Piatt DS.** Underuse of venous thromboembolism prophylaxis for general surgery patients: physician practices in the community hospital setting. Arch Intern Med 1998; 158:1909–1912.
39. **Amin A, Stemkowski S, Lin J, et al.** Thromboprophylaxis rates in US medical centers: success or failure? J Thromb Haemost 2007; 5:1610–1616.
40. **Amin A, Stemkowski S, Lin J, Yang G.** Thromboprophylaxis in US hospitals: adherence to the 6th American College of Chest Physicians' recommendations for at-risk medical and surgical patients. Abstract presented at: 41st Midyear Clinical Meeting of the American Society of Health-System Pharmacists; December 3–7, 2006; Anaheim, CA.
41. **Tapson VF, Decousus H, Pini M, et al.** Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the International Medical Prevention Registry on Venous Thromboembolism. Chest 2007; 132:936–945.
42. **Clarke-Pearson DL, Synan IS, Dodge R, et al.** A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. Am J Obstet Gynecol 1993; 168:1146–1154.
43. **Einstein MH, Pritts EA, Hartenbach EM.** Venous thromboembolism prevention in gynecologic cancer surgery: a systematic review. Gynecol Oncol 2007; 105:813–819.
44. **Clarke-Pearson DL, Synan IS, Hinshaw WM, Coleman RE, Creasman WT.** Prevention of postoperative venous thromboembolism by external pneumatic calf compression in patients with gynecologic malignancy. Obstet Gynecol 1984; 63:92–98.
45. **Ruff RL, Posner JB.** Incidence and treatment of peripheral venous thrombosis in patients with glioma. Ann Neurol 1983; 13:334–336.
46. **Levin JM, Schiff D, Loeffler JS, Fine HA, Black PM, Wen PY.** Complications of therapy for venous thromboembolic disease in patients with brain tumors. Neurology 1993; 43:1111–1114.

Correspondence: *Alex C. Spyropoulos, MD, Chair, Clinical Thrombosis Center, Lovelace Medical Center, 500 Walter Street NE, Suite 301, Albuquerque, NM 87108; alex.spyropoulos@lovelace.com.*

STEVEN B. DEITELZWEIG, MD SYLVIA C. McKEAN, MD ALPESH N. AMIN, MD, MBA
DANIEL J. BROTMAN, MD AMIR K. JAFFER, MD ALEX C. SPYROPOULOS, MD

Prevention of venous thromboembolism in the orthopedic surgery patient

ABSTRACT

Patients undergoing major orthopedic surgery—hip or knee arthroplasty, or hip fracture repair—are in the highest risk category for venous thromboembolism (VTE) solely on the basis of the orthopedic procedure itself. Despite this, nearly half of patients undergoing these procedures do not receive appropriate prophylaxis against VTE, often due to a disproportionate fear of bleeding complications in this population. Guidelines from the American College of Chest Physicians (ACCP) provide evidence-based recommendations for many aspects of VTE risk reduction in the setting of orthopedic surgery, as detailed in this review. The ACCP recommends the use of either low-molecular-weight heparin (LMWH), fondaparinux, or adjusted-dose warfarin as preferred VTE prophylaxis in patients undergoing either hip or knee arthroplasty. Fondaparinux is the preferred recommendation for patients undergoing hip fracture repair, followed by LMWH, unfractionated heparin, and adjusted-dose warfarin as alternative options. Extended-duration prophylaxis (for 4 to 5 weeks) is now recommended for patients undergoing hip arthroplasty or hip fracture repair. Patients undergoing knee arthroscopy do not require routine pharmacologic VTE prophylaxis.

Nearly half of orthopedic surgery patients do not receive appropriate prophylaxis for venous thromboembolism (VTE), as defined by American College of Chest Physicians (ACCP) consensus guidelines, according to a recent analysis of a nationwide database of hospital admissions.[1] Even in teaching hospitals, compliance with consensus guidelines for thromboprophylaxis is suboptimal. In a study of adherence to the ACCP guidelines for VTE prevention among 1,907 surgical patients at 10 teaching hospitals, only 45.2% of hip fracture patients received optimal VTE prophylaxis.[2] Rates of optimal prophylaxis were higher among patients undergoing hip arthroplasty and knee arthroplasty—84.3% and 75.9%, respectively—but were still in need of improvement.[2]

See inside front cover for author affiliations. See end of article for author disclosures.

GROWING INTEREST IN POSTOPERATIVE VTE PROPHYLAXIS AS A QUALITY INDICATOR

As noted in the introductory article in this supplement, the Joint Commission on Accreditation of Healthcare Organizations has taken notice of these shortcomings and has proposed national consensus standards for VTE prevention and treatment.[3] Among its proposed standards are two related to risk assessment and prophylaxis: whether risk assessment/prophylaxis is ordered within 24 hours of hospital admission and within 24 hours of transfer to the intensive care unit.

Other quality-monitoring initiatives are focused specifically on VTE in the surgical population. The Surgical Care Improvement Project (SCIP) has approved two quality measures with respect to VTE prevention: (1) the proportion of surgical patients for whom recommended VTE prophylaxis is ordered, and (2) the proportion of patients who receive appropriate VTE prophylaxis (based on ACCP guideline recommendations) within 24 hours before or after surgery.[4]

In the future, two other VTE-related quality measures from SCIP may be implemented by the Centers for Medicare and Medicaid Services: (1) how often intra- or postoperative pulmonary embolism (PE) is diagnosed during the index hospitalization and within 30 days of surgery, and (2) how often intra- or postoperative deep vein thrombosis (DVT) is diagnosed during the index hospitalization and within 30 days of surgery.[5]

VTE RISK IN ORTHOPEDIC SURGERY

Surgical patients can be stratified into four VTE risk levels—low, moderate, high, and highest—based on age, surgery type, surgery duration, duration of immobilization, and other risk factors.[6] For patients undergoing orthopedic surgery, these levels may be defined according to the following patient and surgical characteristics:

- **Low risk**—surgery duration of less than 30 minutes, age less than 40 years, repair of small fractures
- **Moderate risk**—age of 40 to 60 years, arthroscopy or repair of lower leg fractures, postoperative plaster cast
- **High risk**—age greater than 60 years, *or* age 40 to 60 years with additional VTE risk factors, *or* immobilization for greater than 4 days
- **Highest risk**—hip or knee arthroplasty, hip fracture repair, repair of open lower leg fractures, major trauma or spinal cord injury, or multiple risk factors for VTE (age > 40 years, prior VTE, cancer, or hypercoagulable state).

For patients in the low-risk category, no specific prophylaxis is indicated beyond early and aggressive ambulation.[6] For those in all other risk categories, prophylaxis with pharmacologic anticoagulant agents and/or mechanical devices is indicated, as reviewed below.

All major orthopedic procedures confer highest risk level

Notably, the "highest risk" category includes any patient undergoing hip or knee arthroplasty or hip fracture repair. Among orthopedic surgery patients in this highest-risk category, rates of VTE events in the absence of prophylaxis are as follows:[6]

- Calf DVT, 40% to 80%
- Proximal DVT, 10% to 20%
- Clinical PE, 4% to 10%
- Fatal PE, 0.2% to 5%.

Hip replacement poses greater risk than knee replacement

Within this overall highest-risk category, thromboembolic risk in the absence of prophylaxis differs among procedures. Although patients undergoing hip replacement and those undergoing knee replacement have similar rates of DVT of any type,[6,7] hip replacement is associated with higher rates of the more clinically important events, specifically proximal DVT and PE. In the absence of prophylaxis, proximal DVT occurs in 23% to 36% of hip replacement patients as opposed to 9% to 20% of knee replacement patients; similarly, PE occurs in 0.7% to 30% of hip replacement patients as compared with 1.8% to 7.0% of knee replacement patients.[6,7]

What about bleeding risk?

For many orthopedic surgeons, the risk of bleeding as a result of anticoagulant prophylaxis of VTE looms larger than the risk of VTE itself. This is likely because bleeding, when it does occur, is likely to occur more acutely than VTE does and may directly compromise the result of the operation. For this reason, orthopedic surgeons may be more likely to actually witness bleeding events than VTE events (especially fatal PEs) while their patients are still under their care, leading to a misperception of the relative risks of anticoagulation-related bleeding and thromboembolism.

In reality, rates of major bleeding with pharmacologic prophylaxis of VTE are a tiny fraction of the above-listed rates of VTE events in the absence of prophylaxis in patients undergoing major orthopedic surgery. Reported 30-day rates of major bleeding in patients receiving VTE prophylaxis with heparins range from 0.2% to 1.7%; these rates barely differ from the rates among placebo recipients in the same VTE prophylaxis trials, which range from 0.2% to 1.5%.[8,9] Additionally, within the continuum of risk of major bleeding from various medical interventions, VTE prophylaxis with heparins is one of the lowest-risk interventions, posing far less risk than, for example, the use of warfarin in ischemic stroke patients or in patients older than 75 years.

PHARMACOLOGIC OPTIONS FOR VTE PROPHYLAXIS IN ORTHOPEDIC SURGERY

As reviewed in the introductory article of this supplement, the arsenal of anticoagulants for use in VTE prophylaxis includes low-dose unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) agents such as dalteparin and enoxaparin, and the factor Xa inhibitor fondaparinux. A few additional comments about these and other anticoagulant options is warranted in the specific context of orthopedic surgery.

Fondaparinux. Because most of its formal US indications are for use as VTE prophylaxis in major orthopedic surgery—including hip replacement, knee replacement, and hip fracture repair—fondaparinux has been studied more widely in orthopedic surgery patients than in the other populations reviewed earlier in this supplement. Nevertheless, its use even in these settings has remained somewhat limited. This may be because of concerns over possible increased bleeding risk relative to some other anticoagulants. Because of bleeding risk, fondaparinux is contraindicated in patients who weigh less than 50 kg, and its package insert recommends caution when it is used in the elderly due to an increased risk of bleeding in patients aged 65 or older. Additionally, the Pentasaccharide in Major Knee Surgery (PENTAMAKS) study found fondaparinux to be associated with a significantly higher incidence of major bleeding compared with enoxaparin (2.1% vs 0.2%; $P = .006$) in major knee surgery, although it was superior to enoxaparin in preventing VTE.[10] Other possible reasons for slow adop-

tion of fondaparinux include its long half-life, which results in a sustained antithrombotic effect, its lack of easy reversibility, and a contraindication in patients with renal insufficiency.[11]

Limited role for UFH. Low-dose UFH has a more limited role in orthopedic surgery than in other settings requiring VTE prophylaxis, as current ACCP guidelines for VTE prevention recognize it only as a possible option in hip fracture surgery and state that it is not to be considered as sole prophylaxis in patients undergoing hip or knee replacement.[6]

Warfarin. Although not indicated for use in other VTE prophylaxis settings, the vitamin K antagonist warfarin is recommended as an option for all three major orthopedic surgery indications—knee replacement, hip replacement, and hip fracture repair.[6]

The key to effective prophylaxis with warfarin is achieving the appropriate intensity of anticoagulation. In two separate analyses, Hylek et al demonstrated a balance between safety and efficacy with warfarin therapy targeted to an international normalized ratio (INR) of 2.0 to 3.0.[12,13] An INR greater than 4.0 greatly increased the risk of intracranial hemorrhage, whereas thrombosis was not effectively prevented with an INR less than 2.0.[12,13] This latter point should be stressed to orthopedic surgeons, who sometimes aim for INR values below 2.0.

Although anticoagulation clinics are superior to usual care at maintaining the INR within the window of 2.0 to 3.0, only about one-third of patients nationally who take warfarin receive care in such clinics.[14] Even with optimal care in anticoagulation clinics, some patients will still receive subtherapeutic or supertherapeutic levels of warfarin, which is one of this agent's limitations.

Aspirin not recommended as sole agent. Although aspirin is still used as thromboprophylaxis in orthopedic surgery patients, current ACCP guidelines recommend against its use as the sole means of VTE prophylaxis in any patient group.[6] The limitations of the evidence for aspirin in this setting are illustrated by the Pulmonary Embolism Prevention study, a multicenter randomized trial in patients undergoing hip fracture (n = 13,356) or hip/knee replacement (n = 4,088).[15] Patients received aspirin 160 mg/day or placebo for 5 weeks, starting preoperatively, and were evaluated for outcomes at day 35. Among the hip fracture patients, the rate of symptomatic DVT was lower in the aspirin group than in the placebo group (1.0% vs 1.5%; P = .03), as was the rate of PE (0.7% vs 1.2%, respectively; P = .002), but there was no significant difference in outcomes between the groups among the patients undergoing hip or knee replacement. Notably, 40% of patients in the study also received UFH or LMWH. Further confounding the results, some patients received nonpharmacologic VTE prophylaxis modalities, and others received nonsteroidal anti-inflammatory drugs other than aspirin.

Heparin-induced thrombocytopenia. As noted earlier in this supplement, the incidence of heparin-induced thrombocytopenia (HIT) is markedly higher in patients who receive UFH than in those who receive LMWH. This difference in frequency, which constitutes about a sixfold to eightfold differential, is due to the relationship between standard heparin and platelet factor IV, which can induce formation of IgG antibodies.[16] A 50% or greater reduction in platelet count in heparin recipients should prompt consideration of HIT.

Oral direct thrombin inhibitors. Although the oral direct thrombin inhibitor ximelagatran was rejected for approval by the US Food and Drug Administration (FDA) and recently withdrawn from the market worldwide as a result of hepatic risks, other oral direct thrombin inhibitors are in phase 3 studies for use in orthopedic surgery and may be commercially available options for postoperative VTE prophylaxis before long.

GUIDELINES FOR VTE PROPHYLAXIS IN ORTHOPEDIC SURGERY

The ACCP guidelines referred to throughout this article are widely recognized as a practice standard for VTE prevention and treatment, and have been regularly updated throughout recent decades. The most recent version, issued in 2004, is formally known as the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy.[6] Key orthopedic surgery-related recommendations and notable changes from the previous version of the guidelines, issued in 2001, are outlined below, along with pertinent supportive or illustrative studies.

Hip replacement surgery

For all patients undergoing elective hip replacement surgery, routine use of either LMWH, fondaparinux, or warfarin is recommended (see **Table 1** for recommended dosing). Each of these options is given a Grade 1A recommendation, the guidelines' highest level of endorsement, indicating evidence from randomized controlled trials (RCTs) without important limitations. None of these options is recommended as superior to the other two. The guidelines recommend against the use of any other option, including UFH and mechanical devices, as the sole method of prophylaxis in these patients.[6]

In a change from the previous guidelines, the Seventh ACCP Conference recommends extended prophylaxis, for up to 28 to 35 days after surgery, for

TABLE 1
Options and recommendations for pharmacologic VTE prophylaxis in patients undergoing orthopedic surgery

Procedure	Therapy duration*	Aspirin	Warfarin†	UFH	LMWH	Fondaparinux
Total knee replacement	7–14 days	Not recommended	Dose to INR of 2–3	Not recommended	Enoxaparin 30 mg SC q12h (Dalteparin is not FDA-approved for this indication)	2.5 mg SC once daily
Total hip replacement	4–5 weeks	Not recommended	Dose to INR of 2–3	Not recommended	•Enoxaparin 30 mg SC q12h or 40 mg SC once daily •Dalteparin 5,000 IU SC once daily	2.5 mg SC once daily
Hip fracture surgery	4–5 weeks	Not recommended	Dose to INR of 2–3	5,000 U SC three times daily‡	•Enoxaparin 40 mg SC once daily‡ •Dalteparin 5,000 IU SC once daily‡	2.5 mg SC once daily
Arthroscopy	Need for pharmacologic prophylaxis should be assessed solely on the basis of the patient's individual risk factors for VTE independent of arthroscopy					

* In the United States, routine practice is to initiate prophylaxis for these indications 12 to 24 hours postoperatively.

† Clinical data from randomized controlled trials and observational studies suggest slightly lower efficacy for VTE prophylaxis in orthopedic surgery patients with warfarin compared with LMWH or fondaparinux.

‡ Not FDA-approved for use in hip fracture surgery.

VTE = venous thromboembolism; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; INR = international normalized ratio; SC = subcutaneously

patients undergoing hip replacement or hip fracture surgery. For hip replacement surgery, this is a Grade 1A recommendation for prophylaxis with either LMWH or warfarin and a Grade 1C+ recommendation ("no RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies") for prophylaxis with fondaparinux.[6]

The compelling evidence base for extended prophylaxis with LMWH in this setting was demonstrated in a systematic review of six double-blind, randomized, placebo-controlled trials, as illustrated in **Figure 1**.[17] Additionally, a Belgian cost-utility analysis in patients who underwent total hip or knee replacement showed that extended prophylaxis with enoxaparin (30 days) carried an incremental cost of $6,386 (US dollars) per quality-adjusted life-year compared with standard-duration enoxaparin prophylaxis (12 days), a cost that was well below the "willingness to pay" threshold of $18,200 per quality-adjusted life-year used in European guidelines for cost-effectiveness.[18]

Knee replacement surgery

The same three anticoagulant options that received Grade 1A recommendations for patients undergoing total hip replacement—LMWH, fondaparinux, and adjusted-dose warfarin—are also given Grade 1A recommendations as routine thromboprophylaxis in patients undergoing elective knee replacement (see **Table 1** for dosing). In addition, optimal use of intermittent pneumatic compression devices is recommended as an alternative option to anticoagulant prophylaxis in these patients (Grade 1B, indicating a "strong recommendation" based on RCTs with important limitations). Use of UFH as the sole agent for prophylaxis is recommended against.[6]

For both hip and knee replacement surgery, the Seventh ACCP Conference does not endorse superiority of any one of its three recommended prophylaxis options—LMWH, fondaparinux, and adjusted-dose warfarin—over the other two. However, at least four large randomized trials have directly compared LMWH and adjusted-dose warfarin in the setting of arthroplasty—two in total hip replacement surgery[19,20] and two in total knee replacement surgery.[21,22] Each of these four studies found LMWH to be significantly more effective than warfarin in preventing VTE. In three of the four trials, there was no significant difference between the therapies in rates of major bleeding.[19,21,22] In the remaining trial, which was conducted in hip replacement surgery patients and compared postoperative warfarin with dalteparin initiated either immediately before or early after surgery, patients who received preoperative dalteparin initiation (but not those who received postoperative dalteparin initiation) had an increased rate of major bleeding compared with warfarin recipients ($P = .01$).[20]

Hip fracture surgery

The supportive evidence for anticoagulant prophylaxis in hip fracture surgery is less robust than that in hip and knee replacement surgery. As a result, only fondaparinux has a Grade 1A recommendation as routine prophylaxis in patients undergoing hip fracture surgery. Options with less definitive recommendations are LMWH (Grade 1C+), low-dose UFH (Grade 1B), and adjusted-dose warfarin (Grade 2B, indicating a "weak recommendation" based on RCTs with important limitations) (see **Table 1** for dosing of all agents).[6]

These differing recommendations are supported by the double-blind Pentasaccharide in Hip Fracture Surgery Study (PENTHIFRA) of 1,711 consecutive patients undergoing surgery for hip fracture repair.[23] Patients were randomized to at least 5 days of fondaparinux 2.5 mg once daily, initiated postoperatively, or enoxaparin 40 mg once daily, initiated preoperatively. The incidence of DVT or PE by postoperative day 11 was 8.3% in the fondaparinux arm versus 19.1% in the enoxaparin arm, a statistically significant difference ($P < .001$) in favor of fondaparinux. There were no differences between the groups in rates of death or clinically relevant bleeding.

As noted above, the newly added recommendation in the Seventh ACCP Conference for extended prophylaxis, for up to 28 to 35 days after surgery, applies to patients undergoing hip fracture surgery as well as those undergoing hip replacement surgery. In the setting of hip fracture repair, extended prophylaxis is a Grade 1A recommendation with the use of fondaparinux and a Grade 1C+ recommendation with the use of either LMWH or adjusted-dose warfarin.[6]

Lower extremity fractures and trauma

Although lower extremity fractures are very common, the risk of DVT has been poorly studied in this setting. For patients with isolated lower extremity fractures, the Seventh ACCP Conference recommends that clinicians not use thromboprophylaxis routinely (Grade 2A, indicating an "intermediate-strength recommendation" based on RCTs without important limitations).[6]

Trauma patients, in contrast, are well recognized as being at very high risk for DVT and PE. The Seventh ACCP Conference gives a Grade 1A recommendation to thromboprophylaxis for all trauma patients who have at least one risk factor for VTE. LMWH is recommended (Grade 1A) as the agent of choice for this purpose, provided there are no contraindications to its use, and should be administered as soon as safely possible. Mechanical modalities are reserved for trauma patients with active bleeding or high risk for hemorrhage (Grade 1B). The guidelines recommend against use of inferior vena cava (IVC) filters as primary thromboprophylaxis in trauma patients (Grade 1C, indicating an "intermediate-strength recommendation" based on observational studies).[6]

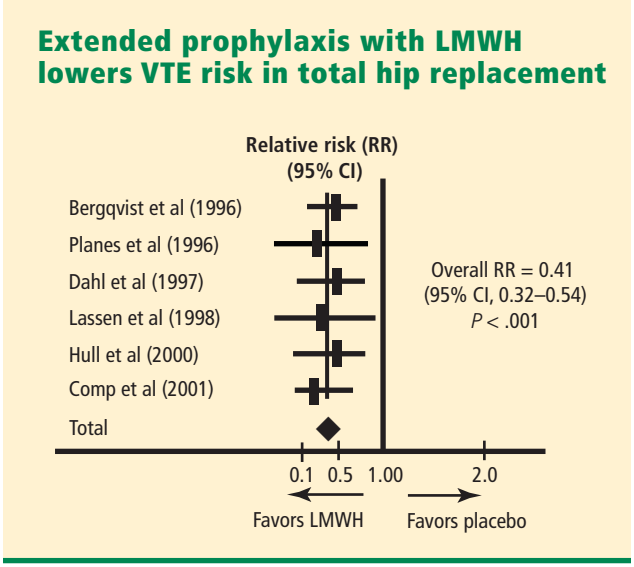


FIGURE 1. Relative risk (and 95% confidence intervals) for all deep vein thrombosis during the out-of-hospital time interval (up to 28 to 35 days after surgery) with extended-duration low-molecular-weight heparin (LMWH) therapy compared with standard-duration LMWH therapy. Results are from six randomized trials of extended prophylaxis in patients undergoing total hip replacement. The risk reduction with extended-duration prophylaxis was statistically significant in all six trials.

Reprinted, with permission, from *Annals of Internal Medicine* (Hull et al, 2001).[17]

Use of ultrasonography

Duplex ultrasonographic screening is recommended in orthopedic trauma patients who are at high risk for VTE and have received suboptimal or no prophylaxis (Grade 1C). In contrast, the Seventh ACCP Conference recommends against routine use of duplex ultrasonography to screen for VTE at hospital discharge in asymptomatic patients following major orthopedic surgery (Grade 1A).[6]

Knee arthroscopy

Arthroscopic knee procedures are increasing in frequency and raise the specter of a potential role for thromboprophylaxis. However, the clinical diagnosis of DVT is unreliable, and even diagnosis by ultrasonography is unreliable following knee arthroscopy, as interpreting scans of veins below the knee is challenging in this setting.[24]

The Seventh ACCP Conference recommends that clinicians not use routine thromboprophylaxis, other than early mobilization, for patients who undergo

Case study: Knee arthroplasty in an obese elderly woman

A 70-year-old woman with osteoarthritis presents for total knee replacement. She is obese (190 lb; 5 ft 7 in) and probably inactive because of her osteoarthritis. She has low-grade bladder cancer, asthma, and gastroesophageal reflux disease. She underwent a total abdominal hysterectomy in the remote past for unclear reasons. Her medications prior to admission are as follows:

- *Oxycodone, 5 mg every 4 hours, with acetaminophen*
- *Calcium carbonate, 250 mg/day*
- *Albuterol, 2 puffs inhaled every 4 hours*
- *Lansoprazole, 30 mg/day.*

She has a remote history of smoking (discontinued 18 years ago) but reports no alcohol or drug abuse.

WHAT IS THIS PATIENT'S RISK FOR VTE?

The risk of VTE in patients undergoing total knee replacement, total hip replacement, or hip fracture repair is significant without prophylaxis or with inadequate prophylaxis. With no prophylaxis, the risk of DVT at 7 to 14 days is 40% to 80% and the risk of proximal DVT detected by venography is 10% to 20%.[6] Although the risk of proximal DVT is most concerning, patients may develop post-phlebitic syndrome, and a prior VTE, even if distal, increases the risk for subsequent events. Another important factor is that there is no way to predict which patients will develop symptomatic DVT.

In addition to the risk associated with the knee replacement procedure, this patient has medical risk factors for VTE, including her advanced age and obesity. According to the Nurses' Health Study, obesity was the most important risk factor for developing PE, and the risk increased consistently with increasing weight.[33] This patient's underlying cancer also confers a twofold to fourfold increase in her risk of VTE.

Diagnosing VTE in a patient recovering from total knee replacement is challenging. The sensitivity of ultrasonography in detecting DVT is lower with total knee replacement than with total hip replacement, at least in the popliteal area, owing to signal interference from the artificial joint and the challenge of clearly imaging the popliteal vein.

What are the options for pharmacoprophylaxis?

The agents that have received Grade 1A recommendations from the Seventh ACCP Conference are LMWH, fondaparinux, and vitamin K antagonists (ie, warfarin).[6] The choice among them hinges on their relative efficacy in clinical trials and their ease of use in the hospital setting. In patients undergoing total knee replacement, reported rates of venographically detected VTE are 46.8% with warfarin prophylaxis, 30.6% with LMWH prophylaxis, and 12.5% with fondaparinux prophylaxis.[25,34]

CASE CONTINUED: DAY OF SURGERY, EARLY POSTOPERATIVE COURSE

The patient is managed within a critical pathway for elective total knee replacement; as such, she receives warfarin 7.5 mg the day before surgery with plans to continue VTE prophylaxis for 3 weeks. Air boots (pneumoboots) and antiembolism stockings are prescribed concurrently.

During the surgery, the patient is unable to tolerate an epidural or femoral nerve catheter. A left femoral nerve

knee arthroscopy (Grade 2B). However, for arthroscopy patients who have inherent risk factors for VTE or who undergo a prolonged or complicated arthroscopy procedure, thromboprophylaxis with LMWH is suggested (Grade 2B).[6]

RECOMMENDED APPROACH TO VTE PROPHYLAXIS IN ORTHOPEDIC SURGERY

Drawing on the ACCP guidelines and the evidence reviewed above, we have outlined our evidence-based recommendations for pharmacologic VTE prophylaxis in patients undergoing orthopedic surgery, as presented in **Table 1**. All patients undergoing major orthopedic surgical procedures (ie, procedures other than arthroscopy) should routinely receive anticoagulant prophylaxis unless they have contraindications to anticoagulation. Recommended agents and their duration of use vary according to the type of surgery, as detailed in **Table 1**.

Extended-duration prophylaxis is recommended for patients undergoing total hip replacement and hip fracture surgery. Aspirin is not recommended as the sole agent for prophylaxis in any orthopedic surgery setting.

Importance of a postoperative prophylaxis protocol

In addition to these broad pharmacologic recommendations, it is important that a postoperative VTE prophylaxis protocol be in place at all hospitals.

At the Ochsner Medical Center in New Orleans, where one of us (S.B.D.) practices, postoperative orders include antithrombotic therapy for surgical patients, starting with placement of thigh-high antiembolism stockings on both legs on the day of surgery for patients undergoing hip replacement and on postoperative day 1 in those undergoing knee replacement. Plantar pneumatic compression devices are applied to both legs in the recovery room and kept on except when the patient is walking. The hospitalist team dictates further

block is attempted without catheter placement. She undergoes general anesthesia with no complications. Her estimated blood loss is 300 mL, and the tourniquet time is 71 minutes.

On the first 2 postoperative days she has difficulty getting out of bed despite a protocol designed to promote walking on postoperative day 1. She experiences agitation on postoperative day 3 and develops a delirium for which she receives pharmacologic treatment. She complains of dysuria on postoperative day 6, and a urinary tract infection is treated with ciprofloxacin.

On postoperative day 7 she complains of fatigue and develops sinus tachycardia (95 to 100 beats per minute). She is presumed to have symptomatic anemia from blood loss, and receives a transfusion for a declining hematocrit level.

On postoperative day 8 she complains of calf pain during the surgical team's morning rounds. She remains tachycardic (95 to 105 beats per minute). Her oxygen saturation is normal and calf ultrasonography is negative. During physical therapy in the afternoon, she has shortness of breath and palpitations while walking. Electrocardiogram reveals atrial fibrillation, for which she is treated with intravenous metoprolol. Chest radiography and cardiac enzyme assessment are negative. Her INR is found to be 2.0. The hospitalist service is called for a medical consultation and recommends a chest computed tomography protocol for PE assessment, which does reveal a PE.

WHAT CLUES MAY HAVE SUGGESTED PE?

The finding of PE is not surprising for a high-risk patient like this with inadequate anticoagulation. A retrospective review of her INR values following the borderline value of 2.0 on postoperative day 8 shows that they were consistently less than 2.0, which is the bottom end of the therapeutic window, since her initial preoperative warfarin dose (7.5 mg). Thus, this patient at very high risk for VTE was not receiving therapeutic prophylaxis for an extended period, which provides the first clue that PE may be accounting for her signs and symptoms.

The development of dyspnea on day 8 is another key clue. Data from the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II)[35] indicate that rapid onset (usually within seconds to hours) of dyspnea at rest is the most common symptom of acute PE, followed by pleuritic chest pain and cough. Signs of PE are nonspecific and include tachypnea and tachycardia, with the latter being a prominent sign in this patient. Notably, PIOPED II found that dyspnea and tachypnea were less frequent in elderly patients with PE who had no previous cardiopulmonary disease.

The precipitating situation is the most important factor to consider when assessing VTE risk.[36] In this case, no further inquiry about additional risk factors would have been required to assign this patient a high pretest probability for acute PE. She had undergone a high-risk surgical procedure that put her at very high risk of VTE.

Calf pain, which she reported the morning of day 8, is also an important clue to PE. In PIOPED II, the symptoms of PE were often accompanied by symptoms of DVT, such as calf or thigh pain, which can help differentiate patients with and without PE.[35]

A careful bedside examination is valuable, including a personally counted respiratory rate, a cardiac examination, and examination of the legs. A new soft systolic murmur of tricuspid regurgitation in an ill patient suggests the possibility of acute PE.

continued on next page

anticoagulation orders. If extended prophylaxis is prescribed, the discharge planner sets up drug delivery and reimbursement, provides a LMWH discharge kit, and teaches the patient to self-inject. If there is concern about increasing swelling at the surgical site while anticoagulant therapy continues, the protocol calls for prompt notification of the responsible physician. To minimize the risk that spinal or epidural hematomas will develop, all agents that increase bleeding propensity should be recognized and ordered accordingly.

SUMMARY

VTE in patients undergoing major orthopedic surgery is a serious health problem that is highly preventable, yet VTE prophylaxis remains underused in this patient population. Despite the availability of practice guidelines for VTE prevention in the orthopedic surgery setting, recommendations are not widely implemented in clinical practice. Recommended prophylactic options differ somewhat among various orthopedic procedures, and the supportive evidence differs for various anticoagulant options.

DISCUSSION: ADDITIONAL PERSPECTIVES FROM THE AUTHORS

Dr. Jaffer: The ACCP recommends against the routine use of aspirin as primary prophylaxis against VTE in major orthopedic surgery, yet orthopedic surgeons across the country still continue to use aspirin in this setting. What are your thoughts on this, Dr. McKean?

Dr. McKean: We agree with the ACCP's recommendation against aspirin as primary VTE prophylaxis in orthopedic patients. The percentage of US knee arthroplasty patients who develop VTE after receiving no prophylaxis at all is roughly 64%; this percentage declines only slightly (to 56%) for knee arthro-

Case study continued

The bottom line is that a diagnosis of PE is difficult and can often be delayed (as in this case), which makes prevention of utmost importance.

CASE CONTINUED: LATER POSTOPERATIVE COURSE

Later on postoperative day 8, a vascular medicine consultation is requested for atrial fibrillation. A vascular surgical consultation is obtained to determine the possible need for an IVC filter. Both consultations conclude that the patient had the acute PE while her INR was in the subtherapeutic range, that there is no need for an IVC filter, and that warfarin dose adjustment to attain an INR of 2.5 (range, 2.0 to 3.0) is important, as is a further 6 months of anticoagulation.

In summary, several postoperative complications occurred. In sequence, the patient became immobile, developed delirium, developed a urinary tract infection, and developed atrial fibrillation, presumably as a result of the PE. Fear of litigation delayed discharge, further prolonging the anticipated 3-day length of stay for knee replacement surgery to 16 days.

WHAT CONTRIBUTED TO THE SUBTHERAPEUTIC LEVEL OF ANTICOAGULATION?

The orthopedic surgeons noted in the chart that the anticoagulation goal was a target INR of 1.7 to 2.3, which represents a common gap between the evidence and clinical practice. To the surgeons, the fear of bleeding was substantial and greater than the fear of fatal PE. The decision about choice of agent and timing of prophylaxis was based on efficacy-to-bleeding tradeoffs; for LMWH, there are only small differences in this tradeoff between starting prophylaxis preoperatively versus postoperatively, whereas warfarin is more difficult to manage. According to a guideline from the American Academy of Orthopaedic Surgeons, the proper duration of anticoagulation following total knee replacement is at least 10 days.[37]

From the internal medicine perspective, it is critical to recognize that guideline-based, in-hospital VTE prophylaxis can reduce the community-based VTE rate for up to 3 months following hospitalization or outpatient surgery. With regard to choice of anticoagulant, LMWH is preferred over warfarin. Warfarin is difficult to manage in postoperative states because of its numerous drug-drug interactions (including ciprofloxacin and perhaps others in this patient's case) and the difficulty of reliably predicting dosing. In this patient, acute PE occurred when the INR was subtherapeutic; for adequate prophylaxis, the target should have been in the range of 2.0 to 3.0, or perhaps 2.0 to 2.5 if bleeding was greatly feared.

Thus, the problem stemmed from a lack of consensus between the surgical and medical teams on the optimal target INR in the postoperative setting. This case exemplifies the different perspectives that orthopedic surgeons and medical consultants bring to the bedside. Orthopedic surgeons rarely encounter acute PE as a complication of their procedures, so their natural fear and most encountered complication is a bleeding episode that can impair the result of an operation. It must be kept in mind, however, that many fewer patients die from bleeding than from acute PE, which is the leading cause of preventable hospital-acquired death.

CONCLUSIONS

The higher a patient's risk of VTE, the greater the reliance on pharmacologic prophylaxis. Aspirin or low-dose UFH have no clear benefit for prophylaxis in hip or knee arthroplasty. LMWH is more efficacious than warfarin in these settings. Fondaparinux has been shown to be more efficacious than LMWH as prophylaxis in hip fracture repair and knee arthroplasty, but it may be associated with more bleeding. The recommended duration of prophylaxis depends on the type of surgery—as well as the patient's response to surgery and whether complications develop (eg, prolonged immobility, dehydration, infection)—as the risk of VTE extends beyond discharge.

plasty patients who receive prophylaxis with aspirin.[25] Since we clearly want to reduce VTE risk as much as possible, I would not use aspirin alone. I would use it only if the patient were already on aspirin, but then I would add either LMWH or fondaparinux.

Dr. Jaffer: Warfarin is another agent that is widely used for prophylaxis in major orthopedic surgery. In fact, the large registries of VTE prevention in major orthopedic surgery suggest that the use of warfarin may be slightly higher than the use of LMWH. If clinicians choose to use warfarin in their practice, what are your recommendations, Dr. Deitelzweig?

Dr. Deitelzweig: As primary prophylaxis for orthopedic surgery patients, warfarin must be dosed to achieve an INR of 2.0 to 3.0; the need for a value in this range is unequivocal. This is a challenging target to attain in the hospital setting.

Dr. Brotman: A study I was involved with a few years ago suggested that warfarin may be inadequate for VTE prevention in the first few days after orthopedic surgery.[26] Orthopedic surgeons at the Cleveland Clinic, where I was practicing at the time, routinely used systematic ultrasonography to assess for thrombosis on postoperative day 2 or 3 following hip or knee arthroplasty, so we conducted a secondary analysis of a case-control study in these ultrasonographically

screened arthroplasty patients to assess rates of early VTE and look for any associations with the type of prophylaxis used. We found that there was about a tenfold increase in the risk of VTE, both distal and proximal, on postoperative day 2 or 3 among patients who received warfarin compared with those who received LMWH. We concluded that warfarin's delayed antithrombotic effects may not provide sufficient VTE prophylaxis in the immediate postoperative setting.[26]

Dr. Deitelzweig: That's a good point. Although it's important to achieve a therapeutic level of warfarin, we now have evidence that it takes some time to achieve that level, and in the interim, bad things can happen to patients.

Dr. Jaffer: Orthopedic surgery encompasses several types of procedures. Dr. Amin, which specific orthopedic surgery patients stand to benefit from extended prophylaxis, and how long should extended prophylaxis last?

Dr. Amin: Major orthopedic surgery comprises hip fracture repair, total hip replacement, and total knee replacement. For hip fracture, there are strong data to support the use of extended prophylaxis with fondaparinux 2.5 mg/day, which showed about an 88% relative reduction in the risk of symptomatic VTE compared with standard-duration fondaparinux (6 to 8 days) followed by matching placebo for the extended phase.[27] The total duration of fondaparinux therapy in the extended-duration arm was 4 to 5 weeks.

Likewise, data support extended prophylaxis in hip arthoplasty patients, for whom the recommended duration is also 4 to 5 weeks. The systematic review by Hull et al[15] demonstrated a 0.41 relative risk of DVT with extended-duration LMWH prophylaxis versus placebo in hip replacement patients **(Figure 1)**, which was a highly statistically significant result.

In contrast, we don't yet have good data to support extended prophylaxis for patients undergoing total knee replacement, which is a bit surprising. In this setting, prophylaxis is recommended for 7 to 14 days but not beyond that.

Dr. Jaffer: Arthroscopy is probably the most common orthopedic procedure performed in the United States today. Dr. Brotman, what is the role of prophylaxis in patients undergoing arthroscopy?

Dr. Brotman: Minor surgery such as arthroscopy can typically be performed safely without routine prophylaxis, other than having the patient ambulate as soon as possible after the procedure. There may be exceptions to this rule, however. I believe that there is potentially a role for pharmacologic prophylaxis in arthroscopy patients who have major risk factors for VTE, such as a personal history of VTE, or who are not expected to become mobile again in a normal rapid fashion after the operation, but prophylaxis has not been studied systematically in such patients.

Dr. Jaffer: Dr. Spyropoulos, there are several new anticoagulants in the pipeline, specifically agents such as the oral direct factor Xa inhibitors and the direct thrombin inhibitors. What do recent clinical trials suggest with regard to the efficacy of these two drug classes for thromboprophylaxis in major orthopedic surgery?

Dr. Spyropoulos: The agents with the most available data are the oral direct factor Xa inhibitors apixaban and rivaroxaban and the oral direct thrombin inhibitor dabigatran. For prophylaxis in orthopedic surgery populations, phase 2 studies have been completed for apixaban and phase 3 trials have been completed for rivaroxaban and dabigatran.

It appears that the factor Xa inhihibitors, apixaban and rivaroxaban, are efficacious in comparison with both dose-adjusted warfarin and LMWH, which is the gold standard for this group of patients.[28,29] So these indeed appear to be promising agents. Rivaroxaban has been submitted to European regulatory agencies for approval for the prevention of VTE in patients undergoing major orthopedic surgery, and its developer plans to submit it to the FDA in 2008 for a similar indication in the United States.

The data are more equivocal with dabigatran. There have been several positive phase 3 studies in orthopedic surgery comparing two dabigatran dosing schemes, 150 and 220 mg once daily, with the European regimen of enoxaparin (40 mg once daily),[30] but a recent study that compared these doses with the North American enoxaparin regimen (30 mg twice daily) failed to meet the criteria for noninferiority.[31] Further clinical trial development is necessary for dabigatran, although in January 2008 the European Medicines Agency recommended its marketing approval for thromboprophylaxis in patients undergoing orthopedic procedures.[32]

I believe that in the next 3 to 5 years our armamentarium will see the addition of at least one, if not more, of these new agents that offer the promise of oral anticoagulation with highly predictable pharmacokinetics and pharmacodynamics and no need for monitoring.

AUTHOR DISCLOSURES

Drs. Deitelzweig and McKean each reported that they have received honoraria for teaching/speaking from Sanofi-Aventis. **Dr. Amin** reported that he has received research funding and honoraria for speaking from Sanofi-Aventis, Eisai, and GlaxoSmithKline. **Dr. Brotman** reported that he has no financial relationships with commercial interests that are relevant to this article. **Dr. Jaffer** reported that he has received consulting fees and honoraria for teaching/

speaking from Sanofi-Aventis, consulting fees and research grant support from AstraZeneca, and consulting fees from Roche Diagnostics and Boehringer Ingelheim; he also serves on the governing board of the Society for Perioperative Assessment and Quality Improvement (SPAQI) and the board of directors of the Anticoagulation Forum. **Dr. Spyropoulos** reported that he has received consulting fees from Sanofi-Aventis, Eisai, and Boehringer Ingelheim.

Each author received an honorarium for participating in the roundtable that formed the basis of this supplement. The honoraria were paid by the Cleveland Clinic Center for Continuing Education from the educational grant from Sanofi-Aventis underwriting this supplement. Sanofi-Aventis had no input on the content of the roundtable or this supplement.

REFERENCES

1. **Yu HT, Dylan ML, Lin J, Dubois RW.** Hospitals' compliance with prophylaxis guidelines for venous thromboembolism. Am J Health Syst Pharm 2007; 64:69–76.
2. **Stratton MA, Anderson FA, Bussey HI, et al.** Prevention of venous thromboembolism: adherence to the 1995 ACCP consensus guidelines for surgical patients. Arch Intern Med 2000; 160:334–340.
3. National Consensus Standards for Prevention and Care of Venous Thromboembolism (VTE). The Joint Commission Web site. http://www.jointcommission.org/PerformanceMeasurement/PerformanceMeasurement/VTE.htm. Accessed January 8, 2008.
4. Surgical Care Improvement Project. MedQIC Web site. http://www.medqic.org/scip/. Accessed January 8, 2008.
5. SCIP process and outcome measures, October 2005. MedQIC Web site. http://www.medqic.org. Accessed January 1, 2007.
6. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 Suppl):338S–400S.
7. **Zimlich RH, Fulbright BM, Friedman RJ.** Current status of anticoagulation therapy after total hip and total knee arthroplasty.J Am Acad Orthop Surg 1996; 4:54–62.
8. **Planes A, Vochelle N, Mazas F, et al.** Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. Thromb Haemost 1988; 60:407–410.
9. **Colwell CW Jr, Spiro TE, Trowbridge AA, et al.** Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. Clin Orthop Relat Res 1995; 321:19–27.
10. **Bauer KA, Eriksson BI, Lassen MR, Turpie AG.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001; 345:1305–1310.
11. **Turpie AGG.** Pentasaccharide Org31540/SR90107A clinical trials update: lessons for practice. Am Heart J 2001; 142(Suppl):S9–S15.
12. **Hylek EM, Singer DE.** Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994; 120:897–902.
13. **Hylek EM, Skates SJ, Sheehan MA, Singer DE.** An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996; 335:540–546.
14. **Samsa GP, Matchar DB, Goldstein LB, et al.** Quality of anticoagulation management among patients with atrial fibrillation: review of medical records from 2 communities. Arch Intern Med 2000; 160:967–973.
15. **PEP Trial Collaborative Group.** Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355:1295–1302.
16. **Warkentin TE.** Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haemotol 2003; 121:535–555.
17. **Hull RD, Pineo GF, Stein PD, et al.** Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med 2001; 135:858–869.
18. **Haentjens P, De Groote K, Annemans L.** Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement: a cost-utility analysis. Arch Orthop Trauma Surg 2004; 124:507–517.
19. **Colwell CW Jr, Collis DK, Paulson R, et al.** Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty: evaluation during hospitalization and three months after discharge. J Bone Joint Surg Am 1999; 81:932–940.
20. **Hull RD, Pineo GF, Francis C, et al.** Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. Arch Intern Med 2000; 160:2199–2207.
21. **Leclerc JR, Geerts WH, Desjardins L, et al.** Prevention of venous thromboembolism after knee arthroplasty: a randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med 1996; 124:619–626.
22. **Fitzgerald RH Jr, Spiro TE, Trowbridge AA, et al.** Prevention of venous thromboembolic disease following primary total knee arthroplasty: a randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am 2001; 83-A:900–906.
23. **Eriksson BI, Bauer KA, Lassen MR, Turpie AG, Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study.** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001; 345:1298–1304.
24. **Demers C, Marcoux S, Ginsberg JS, Laroche F, Cloutier R, Poulin J.** Incidence of venographically proved deep vein thrombosis after knee arthroscopy. Arch Intern Med 1998; 158:47–50.
25. **Geerts WH, Heit JA, Clagett GP, et al.** Prevention of venous thromboembolism. Chest 2001; 119(1 Suppl):132S–175S.
26. **Brotman DJ, Jaffer AK, Hurbanek JG, Morra N.** Warfarin prophylaxis and venous thromboembolism in the first 5 days following hip and knee arthroplasty. Thromb Haemost 2004; 92:1012–1017.
27. **Eriksson BI, Lassen MR; Pentasaccharide in Hip-Fracture Surgery Plus Investigators.** Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 2003; 163:1337–1342.
28. **The Botticelli Investigators.** Late-breaking clinical trial: a dose-finding study of the oral direct factor Xa inhibitor apixaban in the treatment of patients with acute symptomatic deep vein thrombosis [abstract]. Presented at the 21st Congress of the International Society on Thrombosis and Haemostasis; Geneva, Switzerland; July 2007.
29. **Fisher WD, Eriksson BI, Bauer KA, et al.** Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies. Thromb Haemost 2007; 97:931–937.
30. **Haas S.** New oral Xa and IIa inhibitors: updates on clinical trial results. J Thromb Thrombolysis 2008; 25:52–60.
31. **Friedman RJ, Caprini JA, Comp PC, et al.** Dabigatran etexilate vs enoxaparin in preventing venous thromboembolism following total knee arthroplasty. Presented at: 2007 Congress of the International Society on Thrombosis and Haemostasis; July 7–13, 2007; Geneva, Switzerland.
32. Committee for Medicinal Products for Human Use summary of positive opinion for Pradaxa [news release]. London, UK: European Medicines Agency. January 24, 2008. http://www.emea.europa.eu/pdfs/human/opinion/Pradaxa_3503008en.pdf. Accessed February 21, 2008.
33. **Goldhaber SZ, Grodstein F, Stampfer MJ.** A prospective study of risk factors for pulmonary embolism in women. JAMA 1997; 277:642–645.
34. **Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies.** Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. Arch Intern Med 2002; 162:1833–1840.
35. **Stein PD, Beemath A, Matta F, et al.** Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med 2007; 120:871–879.
36. **Goldhaber SZ.** Diagnosis of acute pulmonary embolism: always be vigilant. Am J Med 2007; 120:827–828.
37. American Academy of Orthopaedic Surgeons Clinical Guideline on Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty: Summary of Recommendations. http://www.aaos.org/Research/guidelines/PE_summary.pdf. Accessed December 10, 2007.

Correspondence: *Steven B. Deitelzweig, MD, Vice President of Medical Affairs and Chairman, Department of Hospital Medicine, Ochsner Health System, 1514 Jefferson Highway, New Orleans, LA 70121; sdeitelzweig@ochsner.org.*