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Applying Quality Measures and Guidelines in the Management of Acute Coronary Syndrome and Venous Thromboembolism

Michael P. Gulseth, PharmD, BCPS

Piotr Sobieszczyk, MD

John Fanikos, RPh, MBA

Randall D. Seifert, PharmD

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Editor-in-Chief

Frederic R. Curtiss, PhD, RPh, CEBS
830.935.4319, fcurtiss@amcp.org

Managing Editor

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istefanski@amcp.org

Peer Review Administrator

Jennifer A. Booker, 703.317.0725
jmcpreview@amcp.org

Graphic Designer

Leslie C. Goodwin, 703.845.5404
lgoodwin@amcp.org

July Supplement Editor

Peter Whittaker, PhD

Account Manager

Peter Palmer, 800.486.5454, ext. 13
peter@promedgroup.net

Publisher

Judith A. Cahill, CEBS
Executive Director
Academy of Managed Care Pharmacy

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FACULTY

Michael P. Gulseth, PharmD, BCPS, is currently an Assistant Professor at the University of Minnesota College of Pharmacy, Duluth. In this role, he also serves as a Clinical Specialist for Anticoagulation Services at St. Mary's Medical Center, also in Duluth. Gulseth graduated with his Doctor of Pharmacy degree in 1999 from North Dakota State University in Fargo and then completed residency training at United Hospital in St. Paul, Minnesota. He currently serves as the Chair of Anticoagulation Services for the Saint Mary's/Duluth Clinic Health System and is the lead author and Editor of the American Society of Health System-Pharmacists (ASHP) book, *Managing Anticoagulation Patients in the Hospital: The Inpatient Anticoagulation Service*.

Piotr Sobieszczyk, MD, is the Associate Director of the Cardiac Catheterization Laboratory at Brigham and Women's Hospital (BWH) in Boston and an Instructor in Medicine at the Harvard Medical School. He received his medical degree from Columbia University College of Physicians and Surgeons in New York. He completed his Internal Medicine training at Massachusetts General Hospital and went on to complete fellowships in Cardiovascular Diseases and Interventional Cardiology at BWH. He finished an additional fellowship in Vascular Medicine and Interventional Cardiovascular Medicine. Sobieszczyk is board certified in Internal Medicine, Cardiovascular Diseases, and Interventional Cardiology. He received board certification in Vascular Medicine and Endovascular Interventional Medicine from the American Board of Vascular Medicine. Sobieszczyk's clinical interests span a wide spectrum of venous and arterial diseases, with particular focus on medical and interventional management of carotid, renovascular, and lower-extremity peripheral arterial disease. Additional areas of expertise include complex coronary interventions, percutaneous ventricular assist devices, and percutaneous interventions for structural, valvular, and hypertrophic heart disease. Sobieszczyk's clinical research interests involve development and evaluation of novel endovascular devices for treatment of coronary and noncoronary arterial and venous diseases.

John Fanikos, RPh, MBA, is currently the Assistant Director of Pharmacy at BWH in Boston. He is also Assistant Professor of Clinical Pharmacy Practice at both Northeastern University and Massachusetts College of Pharmacy. He received his BS in Pharmacy from the Massachusetts College of Pharmacy in 1984. He completed an ASHP-accredited residency program at BWH in 1985. He received his MBA from Northeastern University in 1994. He is a member of various professional societies, among them the ASHP, the Massachusetts Society of Health System Pharmacists, and the New England Council of Hospital Pharmacists. Fanikos currently serves as the Chairman of the Voluntary Hospital Association Northeast Clinical Pharmacy Council and has served in this capacity on a national level as well. Currently, he serves on the Board of Directors for the nonprofit organization The North American Thrombosis Forum. Through his pharmacy practice, he has worked with orthopedic, oncology, cardiology, and general medicine patients.

Randall D. Seifert, PharmD, is Senior Associate Dean and Professor, Department of Pharmacy Practice and Pharmaceutical Sciences, University of Minnesota College of Pharmacy, Duluth. Seifert received a BS in Pharmacy at North Dakota State University in 1975, a Doctor of Pharmacy at the University of Minnesota in 1978, and a post-doctoral fellowship in pharmacokinetics at the University of Minnesota and St. Paul-Ramsey Medical Center in 1979. Seifert has experience in managed care, medical group management, clinical research, pharmacy services management, and academics. He has practiced in several settings, including hospital, long-term care, clinical research, medical group management, and managed care. He serves as a consultant to several large multispecialty and independent practice association medical groups in Southern California and Minnesota. Prior to joining the College of Pharmacy faculty, he started and managed a successful consulting company to which he is still affiliated.

Seifert is involved in the development of viable business models for community-based medication therapy management (MTM) services, as well as value propositions for changing health care-based cost management to value management, pharmacoeconomics, and outcomes analysis, researching the impact of ethnic differences in pharmacokinetics and population risk assessment of fixed drug formulations, and evaluating pharmacists' MTM interventions on health economics.

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Target Audience

Managed care professionals including medical directors, managed care executives, pharmacy benefit managers, and others who are involved in health management and research, outcomes management, and pharmacoeconomics.

Learning Objectives

Upon completion of this educational program, the participant will be able to

1. Describe the clinical and economic burden of acute coronary syndrome (ACS) and venous thromboembolism (VTE).
2. Outline current evidence-based guidelines for antiplatelet and anticoagulant therapy in the management of ACS and VTE.
3. Summarize the latest clinical research and its potential impact on antiplatelet and anticoagulant therapy in the management of patients with ACS or VTE.
4. Describe the role of evidence-based guidelines and performance measurement in improving the quality of care for patients with ACS or VTE and the potential role of managed care pharmacists in the implementation of these guidelines and measures.

Synopsis

Acute coronary syndrome (ACS) and venous thromboembolism (VTE) have a substantial clinical and economic impact in the United States. Evidence-based guidelines reflecting recent research findings are available for the management of these conditions, but clinician adherence to these guidelines is less than desired. Antithrombotic therapy plays a vital role in the management of ACS and VTE, but these therapies are complex and not always used appropriately. The federal government and various organizations concerned with the quality of health care in the United States are developing national quality improvement initiatives with performance measures to assess and improve the management of ACS and VTE, as well as their clinical outcomes. Managed care pharmacists can play an important role in ensuring that evidence-based guidelines are incorporated into the managed care plan benefit design, evaluating quality of care using performance measures, and ensuring that steps are taken to improve quality. Also, pharmacists can promote clinician adherence to guidelines and patient adherence to prescribed therapy. Efforts by managed care pharmacists can improve quality of care along with clinical and economic outcomes in patients with ACS or VTE.

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Applying Quality Measures and Guidelines in the Management of Acute Coronary Syndrome and Venous Thromboembolism

Introduction

Michael P. Gulseth, PharmD, BCPS

Acute coronary syndrome (ACS) (ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI]) and unstable angina and venous thromboembolism (VTE) (deep vein thrombosis, pulmonary embolism [PE]) are 2 common conditions causing considerable morbidity and mortality that have a large economic impact in the United States. Heart disease continues to be the leading cause of death in both sexes. More specifically, the incidence of coronary heart disease (CHD) is staggering. For men, 22.8% of those aged 60-79 years have a diagnosis of CHD, and 32.7% of those aged ≥ 80 years carry the diagnosis.¹ For women, 15.4% aged between 60 and 79 years carry a diagnosis of CHD, and 21.6% of those aged ≥ 80 years carry the diagnosis. The incidence of myocardial infarction (MI) continues to be substantial, with nearly 800,000 Americans having had a diagnosed MI by the time they are aged ≥ 65 years.¹

The prevalence of CHD increases with age, and the number of Americans with CHD is expected to increase as the population ages.¹ Patients who survive MI are at increased risk for recurrent MI, angina pectoris, heart failure, stroke, and sudden death.¹

In 2008, the estimated direct and indirect costs of CHD in the United States are \$151.6 billion.¹ This amount is considerably higher than the estimated costs for stroke (\$62.7 billion), hypertensive disease (\$66.4 billion), and heart failure (\$33.2 billion).¹

More than 600,000 Americans develop symptomatic VTE each year, and another 300,000 Americans die of VTE yearly.² The rate of recurrence of VTE is high (17% after 2 years), so prevention of recurrence is an important strategy in managing VTE.³ VTE has been referred to as a silent disease because it is often asymptomatic; therefore, prevention is critical because sudden death can be the first "symptom." Pulmonary hypertension and post-thrombotic syndrome (a painful chronic condition characterized by leg swelling, skin induration, and sometimes

venous stasis ulcers) are common long-term consequences of VTE.^{4,5} Annually, 800,000 patients will develop post-thrombotic syndrome.^{5,6} Estimated annual costs of hospitalization and follow-up treatment for patients with VTE is \$1.5 billion in the United States.⁷ Overall, appropriate management of ACS and VTE is a concern because of the high morbidity, mortality, and costs associated with these conditions. Fatal PE may be the most common preventable cause of hospital death.⁸

Anticoagulant therapies play an important role in the management of ACS and VTE. Problems with anticoagulation therapies and avoidable morbidity and mortality caused by VTE have prompted the federal government and various national organizations concerned with health care quality to focus attention on the proper use of anticoagulant therapies for the prevention and treatment of VTE and management of ACS. These organizations include the Leapfrog Group, National Quality Forum (NQF), The Joint Commission (JC), Agency for Healthcare Research and Quality, and the American Public Health Association. The 2 organizations whose efforts should be noted here are the NQF and The JC.

The NQF is a public-private, not-for-profit organization created to develop and implement a national strategy for health care quality measurement and reporting. The JC (formerly known as the Joint Commission on Accreditation of Healthcare Organizations, or JCAHO) is an independent, not-for-profit organization that establishes standards and accredits hospitals and other health care facilities with the goal of improving the quality and safety of care provided by these institutions. The NQF and The JC are collaborating to develop national consensus standards for the prevention and care of VTE.⁹ These standards address VTE prevention, treatment, and outcomes. The prevalence, morbidity, mortality, and risk factors associated with VTE are reviewed in the second article titled "Guidelines and Performance Measures for the Prevention and Treatment of Venous Thromboembolism." Rates of adherence to evidence-based guidelines for VTE prophylaxis and treatment, as well as efforts to raise awareness and address the problem of VTE, including strategies to promote VTE prophylaxis, also are discussed. Further, optimal treatment of VTE is reviewed.

The Surgical Care Improvement Project (SCIP) is a national hospital-based quality improvement initiative led by the Centers for Medicare & Medicaid Services (CMS) to reduce the rate of adverse outcomes from common surgical procedures, including VTE.¹⁰ The proper use and timing of VTE prophylaxis before surgery and the incidence of VTE during or within 30 days after surgery are among SCIP measures.¹¹ Reporting data for these measures to the CMS by health care institutions will be required

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Author

MICHAEL P. GULSETH, PharmD, BCPS, at the writing of this article, was Assistant Professor at the University of Minnesota College of Pharmacy in Duluth.

AUTHOR CORRESPONDENCE: Michael P. Gulseth, PharmD, BCPS, Assistant Professor, University of Minnesota College of Pharmacy, Duluth, 127 Life Science, 1110 Kirby Dr., Duluth, MN 55811. Tel.: 218.726.6012; Fax: 218.726.6500; E-mail: mgulseth@umn.edu

to obtain full reimbursement from the CMS. The data also will become part of Hospital Compare, a CMS database designed to allow consumers to compare the quality of care provided at various health care institutions.

Evidence-based guidelines are available from the American College of Chest Physicians (ACCP) for the prevention and treatment of VTE, as well as the American College of Cardiology (ACC) and the American Heart Association (AHA), for the management of ACS.¹²⁻¹⁵ Recent updates to the ACS guidelines from the ACC/AHA reflect the results of recent studies comparing therapeutic regimens involving antiplatelet and anticoagulant therapies.^{16,17} Revised guidelines from the ACCP for the use of antithrombotic therapy were recently published. The first article in this supplement titled "Guidelines and Performance Measures for the Management of Acute Coronary Syndrome" characterizes the pathophysiology of ACS and describes the ACC/AHA guidelines for reperfusion therapy in patients with STEMI; the use of antiplatelet and anticoagulant therapies for the treatment of STEMI, NSTEMI, and unstable angina, including patients who undergo percutaneous coronary intervention; and long-term antiplatelet therapy after an ACS episode.

The development of national quality improvement initiatives designed to improve VTE prophylaxis and the use of antiplatelet and anticoagulant therapies along with the recent changes in evidence-based guidelines for the management of ACS have important implications for managed care pharmacists. For example, managed care plan benefits should be designed to optimize the use of drug therapies to minimize the morbidity, mortality, and costs associated with these common conditions. In addition, managed care pharmacists can use various strategies to improve quality of care and clinical outcomes and also reduce costs in patients with ACS and VTE by improving clinician adherence to evidence-based treatment guidelines and patient adherence to the treatment plan. The third article titled "Management of Acute Coronary Syndrome and Venous Thromboembolism: A Managed Care Perspective" discusses the economic impact of ACS and VTE and highlights factors that contribute to preventable morbidity, mortality, and costs associated with these conditions. Strategies that managed care pharmacists can use to improve clinician adherence to evidence-based treatment guidelines and patient adherence to the treatment plan, thereby improving clinical and economic outcomes, are also addressed.

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Guidelines and Performance Measures for the Management of Acute Coronary Syndrome

Piotr Sobieszczyk, MD

ABSTRACT

BACKGROUND: Acute coronary syndrome (ACS) is caused by reduced perfusion of the myocardium and characterized by chest pain. The primary goals of treatment for ACS are to restore blood flow through occluded coronary arteries and prevent recurrent coronary events. Antiplatelet and anticoagulant therapies play a crucial role in the treatment of ACS by interrupting the thrombotic process.

OBJECTIVES: To characterize the pathophysiology of ACS and to describe the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for reperfusion therapy in patients with ST-segment elevation myocardial infarction (STEMI); the use of antiplatelet and anticoagulant therapies for the treatment of STEMI, non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), including patients who undergo percutaneous coronary intervention (PCI); and long-term antiplatelet therapy after an ACS episode.

SUMMARY: The preferred reperfusion strategy in patients with STEMI is PCI if it can be performed within 90 minutes after arrival at the hospital. Patients with NSTEMI or UA also may undergo PCI. Thrombolysis is an alternative method of reperfusion for patients with STEMI but not for patients with NSTEMI or UA. Dual antiplatelet therapy with aspirin and the thienopyridine clopidogrel is recommended by the ACC/AHA for 12 months in patients with STEMI, NSTEMI, or UA, including patients with coronary stents. Platelet glycoprotein (GP) IIb/IIIa inhibitors are routinely used during PCI in patients with STEMI and NSTEMI. These agents should be used in addition to aspirin and clopidogrel in patients with NSTEMI and elevated troponin levels who undergo coronary intervention. Unfractionated heparin (UFH) or the low-molecular-weight heparin enoxaparin may be used in patients with STEMI undergoing reperfusion with thrombolytic agents or PCI and patients with NSTEMI or UA. There are substantial data on enoxaparin in the ACS arena, but UFH is preferred for patients who undergo coronary intervention because of greater ease of therapeutic monitoring and reversal of anticoagulant effects if bleeding complications arise. The pentasaccharide fondaparinux may become an alternative to UFH and enoxaparin for patients with STEMI and some patients with NSTEMI or UA. Fondaparinux is preferred for patients with NSTEMI or UA who are at increased risk for bleeding when a conservative approach is chosen, but it is not recommended for patients when an early invasive approach is chosen because of the risk of catheter-related thrombi. The direct thrombin inhibitor bivalirudin may be used for anticoagulation in patients with NSTEMI who undergo early invasive procedures, and GP IIb/IIIa inhibitor use may be avoided in some patients; however, upstream antiplatelet therapy with clopidogrel is also needed if these patients undergo PCI. Patients undergoing coronary stenting must receive dual antiplatelet therapy.

CONCLUSIONS: Antiplatelet and anticoagulant therapies for patients with ACS are complex. Evidence-based guidelines facilitate the therapeutic decision-making process for these therapies in patients with ACS.

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■ Pathophysiology and Epidemiology

Acute coronary syndrome (ACS) is a manifestation of coronary heart disease (CHD) that encompasses a spectrum of events in which blood flow to the myocardium is suddenly and severely reduced or completely interrupted: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA). The decrease in myocardial perfusion causes myocardial ischemia that can lead to cell death and myocardial infarction (MI), which may then result in heart failure and death. The classic symptom of ACS is chest pain. Myocardial injury and cell death can be detected by characteristic changes in the electrocardiogram (ECG) and by elevation of the cardiac proteins troponin and creatine kinase in the bloodstream.

The most dangerous of the 3 clinical scenarios is STEMI, which is often associated with sudden death. It accounts for a little more than one third of ACS cases and is caused by the sudden rupture of a cholesterol-filled plaque in the coronary artery wall.¹ Exposure of contents of the plaque to constituents in the bloodstream initiates a cascade of events that culminates in the formation of a thrombus over the plaque. The thrombus completely blocks blood flow through the artery, depriving the myocardium of blood and causing infarction. This complete cessation of blood flow to the myocardium causes characteristic elevations in the ST segments on the ECG and can also result in pathological Q waves.

A similar pathophysiological process occurs in patients with NSTEMI, but blockage of the artery, interruption of blood flow by the thrombus, and myocardial cell injury and death are less extensive than in patients with STEMI. Nevertheless, blood flow to the myocardium can be sufficiently reduced to cause ECG changes and the release of troponin and creatine kinase from injured muscle cells. Similar pathology occurs with UA, yet UA is characterized by chest pain at rest lasting for more than 20 minutes or chest pains that rapidly accelerate in frequency and

Author

PIOTR SOBIESZCZYK, MD, is Associate Director, Cardiac Catheterization Laboratory, Brigham and Women's Hospital, Boston.

AUTHOR CORRESPONDENCE: Piotr Sobieszczyk, MD, Associate Director, Cardiac Catheterization Laboratory, Brigham and Women's Hospital, Cardiovascular Division, PBB-113, 75 Francis St., Boston, MA 02115. Tel.: 617.732.8898; Fax: 617.732.7122; E-mail: psobieszczyk@partners.org

severity. UA is a warning sign of rapidly diminishing blood flow, which may continue to worsen and progress to MI.

■ Treatment

The primary goals of treatment for ACS are to restore blood flow through occluded coronary arteries and prevent recurrent coronary events. Treatment of ACS has evolved over the last several decades. Percutaneous coronary intervention (PCI) is now an integral part of ACS management. The vast majority of patients with ACS undergo PCI with balloon angioplasty to reopen occluded coronary arteries by insertion of a bare-metal or drug-eluting stent in the reopened artery to maintain vessel patency. The urgency of PCI and coronary stenting is dictated by the type of ACS and the clinical condition of the patient.

Medical management of ACS involves antiplatelet and anticoagulant therapies to interrupt the thrombotic process. Reductions in myocardial oxygen demand and potentially lethal arrhythmias are achieved with administration of beta-blockers. Angiotensin-converting enzyme (ACE) inhibitors are used to inhibit ventricular remodeling in the damaged myocardium and prevent the development of heart failure. Nitrates remain the mainstay of therapy for the relief of angina and improvement in myocardial blood flow. Lipid-lowering agents reduce cholesterol levels, decrease plaque formation, and prevent the rupture of existing plaques. Antiplatelet and anticoagulant therapies are the focus of this article.

■ Reperfusion Therapy in Patients with STEMI

In patients with STEMI, time is of the essence because rapid reperfusion reduces damage to the myocardium and the risk of heart failure and death.² Salvage of myocardial tissue depends on the early recognition of symptoms and rapid initiation of therapy.

The 2 strategies commonly used for opening an occluded coronary artery are thrombolysis and PCI with coronary stent deployment. PCI is the preferred reperfusion strategy if cardiac catheterization can be performed within 90 minutes after presentation (Figure 1).² Nevertheless, many patients with STEMI are treated in hospitals without cardiac catheterization facilities, and thrombolysis remains an important method of reperfusion in the United States and worldwide. The goal is to administer thrombolytic therapy early after symptom onset and within 30 minutes after the patient presents to the health care system.² However, thrombolytic agents remain effective when used up to 12 hours after symptom onset.³

■ Ancillary Antiplatelet and Anticoagulation Therapies in Patients with STEMI

After a thrombus is dissolved by thrombolytic therapy and myocardial reperfusion is achieved, plaque contents remain exposed to the bloodstream. This exposure continues to drive the coagulation cascade and induce thrombin deposition, which

promotes platelet aggregation on the plaque, recurrence of thrombus formation, and reocclusion of the coronary artery. Therefore, ancillary antiplatelet and anticoagulation therapies should be administered concurrently with thrombolytic agents.

Antiplatelet Therapies

Antiplatelet therapy has been the cornerstone of ACS management. Aspirin 160 mg-325 mg per day is recommended initially for patients with STEMI.^{2,4} In a placebo-controlled study of patients with suspected STEMI, enteric-coated aspirin 160 mg per day reduced the 5-week cardiovascular mortality rate by 23% compared with placebo.⁵ A nonenteric-coated formulation is recommended for acute events to allow rapid buccal absorption.⁴ Aspirin irreversibly inhibits platelet aggregation by inhibiting the enzyme cyclooxygenase-1, thereby reducing the production of thromboxane A₂, one of several potent platelet activators.⁴ Aspirin 75 mg-325 mg per day should be continued indefinitely in patients with STEMI unless it is contraindicated.² Patients who cannot take aspirin because of an allergy may receive a thienopyridine (e.g., clopidogrel, ticlopidine) instead.

Thienopyridines inhibit platelet aggregation by irreversibly binding to platelet adenosine diphosphate receptors.⁶ Loading doses are needed to provide a prompt antiplatelet effect on the first day of therapy.⁶ Although ticlopidine has been used successfully in patients with STEMI and UA/NSTEMI to prevent coronary stent thrombosis, its use is limited by a high incidence of gastrointestinal (GI) adverse effects and neutropenia.⁷

Clopidogrel does not have the side-effect profile associated with ticlopidine.⁶ Clopidogrel is administered orally as a 300-mg loading dose followed by a 75-mg-per-day maintenance dose. There is new evidence that a larger clopidogrel loading dose of 600 mg-900 mg can be used safely to accelerate full platelet inhibition.^{8,9}

Clopidogrel has been widely used in combination with aspirin after placement of coronary stents or as an alternative to aspirin in patients with ACS. Recent evidence from 2 large randomized, placebo-controlled studies suggests that the combination of aspirin and clopidogrel (dual antiplatelet therapy) is beneficial in patients with STEMI.^{10,11} In the COMMIT trial, >45,000 patients with STEMI were randomly assigned to receive clopidogrel 75 mg per day or placebo for up to 4 weeks or until discharge from the hospital.¹⁰ All patients received aspirin 162 mg per day. The incidence of death, reinfarction, or stroke was significantly lower in the clopidogrel group (9.2%) compared with the placebo group (10.1%, $P=0.002$). All-cause mortality was significantly lower in the clopidogrel group (7.5%) than in the placebo group (8.1%, $P=0.030$). The benefit of clopidogrel was independent of thrombolytic therapy, which was used in 54% of enrollees. No excess risk of cerebral or fatal bleeding was associated with clopidogrel.

In the CLARITY-TIMI 28 trial, 3,491 patients who received thrombolytic therapy within 12 hours after STEMI onset were randomly assigned to receive clopidogrel 300 mg followed by

FIGURE**Use of Antiplatelet and Anticoagulant Therapies in Patients with ST-Segment Elevation Myocardial Infarction** Adapted from Antman et al.²

ACT=activated clotting time; GP=glycoprotein; i.v.=intravenous; PCI=percutaneous coronary intervention; s.c.=subcutaneous; UFH=unfractionated heparin.

75 mg per day or placebo.¹¹ All patients received aspirin 150 mg-325 mg on the first day followed by 75 mg-162 mg per day. The rate of recurrent MI, death, or persistently occluded artery during subsequent coronary angiography was significantly lower in the clopidogrel group (15.0%) than in the placebo group (21.7%, $P<0.001$). Clopidogrel primarily affected the rate of recurrent MI and persistent artery occlusion, not all-cause mortality. The rate of major bleeding after 30 days was similar in the clopidogrel group (1.9%) and the placebo group (1.7%, $P=0.800$).

Results of the CLARITY-TIMI 28 and COMMIT trials suggest that clopidogrel should be administered in combination with aspirin in patients with STEMI regardless of whether thrombolytic agents are used. Current evidence-based guidelines of the American College of Cardiology (ACC) and American Heart

Association (AHA) support this practice, although no data are available to guide decision making about a loading dose of clopidogrel for patients aged ≥ 75 years.² The optimal duration of clopidogrel therapy in patients with STEMI is unclear.² Current ACC/AHA recommendations support a 12-month course of dual antiplatelet therapy.² The increased risk of bleeding associated with dual antiplatelet therapy is a concern in patients who are planning to undergo coronary artery bypass graft (CABG) surgery. Clopidogrel should be withheld for at least 5 days and preferably 7 days before CABG surgery to reduce the risk of operative bleeding.²

Anticoagulant Therapies

Patients undergoing thrombolysis should receive ancillary anticoagulation therapy to reduce the risk of reinfarction.

Unfractionated heparin (UFH) therapy should be administered for a minimum of 48 hours, and enoxaparin and fondaparinux should be used for the duration of hospitalization up to 8 days.² The traditional anticoagulant is UFH, a mixture of polysaccharide chains that promote the activity of circulating antithrombin. Antithrombin, in turn, inactivates thrombin (factor IIa) and factor Xa.¹² UFH prevents thrombus propagation but does not dissolve an existing thrombus. UFH is administered during thrombolysis as an intravenous bolus dose of 60 units per kg (not to exceed 4,000 units) followed by intravenous infusion of 12 units per kg per hour (not to exceed 1,000 units per hour).² The dosage is titrated to maintain an activated partial thromboplastin time (aPTT) 1.5-2.0 times that of a specified control value (50-70 seconds).² Anticoagulants other than UFH are recommended if therapy is continued for more than 48 hours.² Continuing UFH therapy for more than 48 hours increases the risk of heparin-induced thrombocytopenia (HIT), an immune-mediated reduction in platelet count that increases the risk for thrombosis.²

The need for continuous intravenous infusion, frequent laboratory monitoring, and dosage adjustment, as well as difficulty achieving consistent levels of anticoagulation stimulated a search for anticoagulants that are as effective and safe as UFH but easier to use. Chemical or enzymatic modification of UFH yielded low-molecular-weight heparin (LMWH) with smaller polysaccharide chains. LMWH inactivates factor Xa to a greater extent than factor IIa, and it does not prolong the aPTT.¹² The risk for HIT is lower in patients receiving LMWH than in patients treated with UFH.¹² LMWH binds to plasma proteins to a lesser extent than UFH, which improves the predictability of the dose-response relationship.¹² LMWH also has a longer duration of pharmacodynamic effects than UFH. Most LMWH products are administered once or twice daily without need for laboratory monitoring.

The most extensively studied LMWH in patients with STEMI is enoxaparin. In patients aged <75 years and without severe renal impairment, enoxaparin is administered at the time of thrombolysis as a 30-mg intravenous dose followed 15 minutes later by subcutaneous injection of 1 mg per kg every 12 hours for the duration of hospitalization up to 8 days.² Patients aged ≥75 years may be at increased risk for bleeding during enoxaparin therapy; therefore, the initial intravenous dose should be omitted, and a reduced maintenance dosage of 0.75 mg per kg subcutaneously every 12 hours should be used.^{2,13} A maintenance dosage of 1 mg per kg subcutaneously every 24 hours should be used if the estimated creatinine clearance is <30 mL per minute regardless of age.²

Enoxaparin was compared with UFH in a randomized, open-label study of 4,078 patients with STEMI known as ASSENT-3.¹³ Patients received tenecteplase plus enoxaparin 30 mg intravenously followed immediately by 1 mg per kg subcutaneously every 12 hours until hospital discharge or revascularization for

up to 7 days, or they received tenecteplase plus UFH 60 units per kg (not to exceed 4,000 units) as an intravenous bolus followed by 12 units per kg per hour (not to exceed 1,000 units per hour) by intravenous infusion with the dosage adjusted to maintain an aPTT of 50-70 seconds for 48 hours. The incidence of a composite endpoint of 30-day mortality, in-hospital reinfarction, or in-hospital refractory ischemia was significantly lower in the enoxaparin group (11.4%) than in the UFH group (15.4%, $P=0.001$). Similar findings were observed when this composite endpoint included in-hospital intracranial bleeding and in-hospital major bleeding complications (13.7% with enoxaparin vs. 17.0% with UFH, $P=0.008$). However, patients aged ≥75 years who received enoxaparin were at a slightly higher risk for bleeding that was not significant compared with patients of the same age who received UFH. These findings form part of the basis for the ACC/AHA guidelines for enoxaparin dosage reduction to prevent bleeding complications in elderly patients.²

In a more recent randomized, double-blind study known as EXTRACT-TIMI 25, enoxaparin was compared with UFH in more than 20,000 patients with STEMI who were planning to undergo thrombolysis.¹⁴ The ACC/AHA dosing recommendations for enoxaparin in patients aged ≥75 years and younger patients and UFH were followed. The 30-day rate of death or nonfatal recurrent MI was 9.9% in the enoxaparin group and 12% in the UFH group, a difference that is significant ($P<0.001$). The incidence of major bleeding after 30 days was significantly higher in the enoxaparin group (2.1%) than in the UFH group (1.4%, $P<0.001$). When results were stratified by age, the relative risk of major bleeding in patients aged ≥75 years treated with enoxaparin instead of UFH (1.15) was lower than that found in younger patients (1.67).¹⁵

Fondaparinux is a synthetic pentasaccharide that inhibits factor Xa activity, thrombin generation, and thrombus formation by selectively binding to antithrombin III.¹² The drug has a long half-life that allows once-daily administration. In patients with STEMI, fondaparinux is given as an initial 2.5-mg intravenous dose followed by 2.5 mg subcutaneously once daily.² This usage is not approved by the U.S. Food and Drug Administration (FDA).¹⁶ The level of anticoagulation provided by fondaparinux is consistent, and laboratory monitoring is not required. Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL per min) because the drug is eliminated primarily by the kidneys, and patients with severe renal impairment are at increased risk for major bleeding.¹⁶ Currently, no antidote is available to reverse the anticoagulant effects of fondaparinux; therefore, the drug's long half-life may be detrimental when bleeding occurs.

Fondaparinux 2.5 mg intravenously followed by 2.5 mg subcutaneously once daily for up to 8 days was compared with UFH given in accordance with ACC/AHA guidelines for up to 48 hours or with placebo in the OASIS-6 trial, a randomized, double-blind study of more than 12,000 patients with STEMI.¹⁷

Thrombolytic therapy was used in 45% of patients in both treatment groups. The 30-day incidence of death or reinfarction was significantly lower in the fondaparinux group (9.7%) than in the control group (11.2%, $P=0.008$). The incidence of severe hemorrhage was slightly lower in the fondaparinux group (1.0%) than in the control group (1.3%), but the difference was not significant ($P=0.13$).

Fondaparinux has not been compared with LMWH in well-controlled clinical trials of patients with STEMI, nor has its safety in combination with dual antiplatelet therapy been evaluated. At present, the ACC/AHA guidelines provide the strongest support for the use of UFH, enoxaparin, or fondaparinux in patients with STEMI undergoing reperfusion with thrombolytic agents.²

■ Treatment Strategies for NSTEMI/UA

The basic principles of pharmacotherapy for patients with NSTEMI or UA are similar to those for patients with STEMI.¹⁸ Use of beta-blockers, ACE inhibitors, nitrates, and aspirin in patients with NSTEMI or UA is as important as it is in patients with STEMI. The primary difference in treatment regimens for these patient populations lies in the reperfusion strategies.

In patients with NSTEMI or UA, thrombolytic agents are uniformly harmful. The partly blocked coronary artery is treated with a combination of antiplatelet agents and anticoagulants. The goal of this approach is to stabilize the ruptured plaque and prevent complete occlusion of the coronary vessel by interrupting the coagulation cascade and preventing thrombus progression. The intensity of anticoagulation can be increased if the clinical status worsens.

In the United States, most patients with NSTEMI or UA undergo cardiac catheterization within the first 24-48 hours after presentation; therefore, the compatibility of the anticoagulants used during this initial period with the needs of the cardiac catheterization laboratory is a consideration. The desired characteristics of anticoagulants used in the cardiac catheterization laboratory differ from those used in the medical management of NSTEMI or UA.

A system for predicting the risk for death and ischemic events in patients with NSTEMI or UA known as the Thrombolysis in Myocardial Infarction (TIMI) risk scoring system has been developed based on clinical trial data in this patient population.¹⁹ This risk scoring system is one of several systems for risk stratification that are used for planning therapeutic strategies in patients with NSTEMI or UA based on risk. In the TIMI risk scoring system, 1 point is given to each of 7 variables: aged ≥ 65 years, at least 3 CHD risk factors, prior coronary stenosis $\geq 50\%$, ST-segment deviation on the ECG at time of presentation, at least 2 anginal events in the preceding 24 hours, use of aspirin in the preceding 7 days, and elevated serum cardiac markers. A patient's TIMI risk is categorized based on the number of points as low (0-2), medium (3-4), or high (5-7). Patients with

NSTEMI or UA and a low TIMI risk score are usually evaluated in the emergency department using serial biochemical marker measurements. Patients with negative test results typically are admitted to a general floor of the hospital with telemetry monitoring, and they may undergo stress testing to ascertain the need for cardiac catheterization. Most patients with NSTEMI or UA and a medium or high TIMI risk score are admitted to a coronary intensive care unit, chest pain unit, or general floor depending on the perceived risk. High-risk patients undergo early PCI and revascularization if stenosis is found. Most moderate-risk patients also undergo PCI and revascularization during the hospital stay, although patients without MI may have a stress test before PCI.

Antiplatelet Therapies

Guidelines for the management of NSTEMI and UA that address antiplatelet and anticoagulant therapies have been published by the ACC and AHA.¹⁸ Three types of antiplatelet agents are used in NSTEMI or UA: aspirin, thienopyridines, and platelet glycoprotein (GP) IIb/IIIa inhibitors.

Aspirin should be administered as soon as possible in the course of medical evaluation of patients with NSTEMI or UA regardless of whether they plan to undergo cardiac catheterization.¹⁸ The recommended initial dosage is 162 mg-325 mg per day in an oral or chewable nonenteric formulation.¹⁸ Aspirin 75 mg-325 mg per day should be continued indefinitely in patients without aspirin intolerance or hypersensitivity.¹⁸ Patients with aspirin intolerance or hypersensitivity should receive clopidogrel 300 mg-600 mg as a loading dose followed by 75 mg per day instead of aspirin.¹⁸ Patients with a history of GI bleeding may benefit from addition of a proton pump inhibitor to reduce the risk of bleeding during treatment with aspirin or clopidogrel.¹⁸

In a randomized, double-blind, placebo-controlled study of more than 12,000 patients with NSTEMI or UA known as the CURE trial, a 300-mg loading dose of clopidogrel followed by 75 mg per day for 3-12 months was associated with a significant reduction in the incidence of death from cardiovascular causes, nonfatal MI, or stroke (9.3% vs. 11.4% in the placebo group, $P<0.001$).²⁰ All patients received aspirin 75 mg-325 mg per day. A significantly higher incidence of major bleeding was associated with clopidogrel (3.7%) compared with placebo (2.7%, $P=0.001$). These findings form part of the basis for the practices recommended in the ACC/AHA guidelines of withholding clopidogrel for at least 5 days before CABG surgery and continuing the drug for 12 months in patients with NSTEMI or UA.^{2,18}

The GP IIb/IIIa receptor is ubiquitous on the platelet surface. Fibrinogen binds to the receptor on multiple activated platelets, causing platelet aggregation regardless of what pathway led to platelet activation (i.e., the GP IIb/IIIa receptor is the final common pathway for platelet aggregation). The receptor is blocked by GP IIb/IIIa inhibitors, preventing platelet aggregation.

Three GP IIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) are available in the United States. Platelet inhibition from GP IIb/IIIa inhibitors begins promptly after initiation of drug therapy. Stopping eptifibatide and tirofiban, but not abciximab, infusion returns platelet function to normal within several hours after discontinuation of therapy.^{21,22}

GP IIb/IIIa inhibitors have been evaluated primarily in patients with NSTEMI or UA who undergo PCI. Support for the use of GP IIb/IIIa inhibitors in patients with NSTEMI or UA who are initially treated conservatively with medical therapy is agent specific. Abciximab should not be used in patients with NSTEMI or UA if a conservative medical strategy is planned. The drug is approved by the FDA only as an adjunct to PCI.²¹ Patients with NSTEMI or UA who have high-risk features, worsening symptoms, or in whom coronary angiography is considered but will be delayed should receive eptifibatide or tirofiban instead of abciximab.¹⁸

Eptifibatide and tirofiban are approved by the FDA for use in combination with aspirin and UFH for the management of patients with NSTEMI or UA who are treated medically or invasively.^{22,23}

Anticoagulant Therapies

Every patient presenting with NSTEMI or UA should be treated with an anticoagulant in addition to antiplatelet therapy. The choice of anticoagulant often depends on whether and when cardiac catheterization is planned.

The anticoagulant with the longest history of use in patients with NSTEMI or UA is UFH. In the Antithrombotic Therapy in Acute Coronary Syndromes study of 214 patients with NSTEMI or UA, UFH plus aspirin reduced the 14-day incidence of recurrent angina with ECG changes, MI, or death from 27% with aspirin alone to 10.5% with combination therapy ($P=0.004$).²⁴

UFH is administered as a weight-based intravenous bolus dose followed by maintenance intravenous infusion, with a goal aPTT between 50 and 70 seconds.¹⁸ The advantage of UFH lies in the ease of regulating its anticoagulant effect during cardiac catheterization. The level of anticoagulation can be easily monitored with a rapid point-of-care assay, the activated clotting time (ACT). There is considerable experience with the use of UFH in the cardiac catheterization laboratory. Its anticoagulant effects can be readily reversed with protamine if bleeding complications arise.

The use of enoxaparin in patients who proceed to the cardiac catheterization laboratory is more problematic than UFH. There is no reliable, widely available point-of-care testing to monitor the anticoagulant effects of enoxaparin, and these effects are much less reversible with protamine than are the effects of UFH.²⁵

The use of enoxaparin and UFH was compared in the SYNERGY trial, a randomized, open-label study of more than 10,000 patients with NSTEMI who planned to undergo an early invasive strategy.²⁶ Patients were randomly assigned to receive

enoxaparin 1 mg per kg subcutaneously every 12 hours or UFH 60 units per kg (not to exceed 5,000 units) intravenously followed by 12 units per kg per hour (not to exceed 1,000 units per hour) intravenously. Platelet GP IIb/IIIa inhibitors also were used during coronary interventions. There was no significant difference between enoxaparin and UFH in the 30-day incidence of death or nonfatal MI (14.0% and 14.5%, respectively; $P=0.400$). A significantly higher incidence of TIMI major bleeding at 30 days was associated with enoxaparin (9.1%) compared with UFH (7.6%, $P=0.008$). In patients who received the same therapy consistently throughout the SYNERGY study (i.e., no crossover to heparin or vice versa), enoxaparin significantly reduced the 30-day incidence of death or nonfatal MI by 18% from 15.9% in the UFH group to 13.3% in the enoxaparin group. Seventeen percent of patients in both treatment groups required transfusions. Therefore, some say it is prudent to adhere to a consistent anticoagulation strategy before and during cardiac catheterization in patients with NSTEMI or UA (i.e., use UFH in patients scheduled to undergo cardiac catheterization). On the other hand, many interventionalists are much more comfortable using UFH, and any use of other therapies risks a crossover and could affect outcomes in a negative way, such as the outcomes of those patients who crossed over in this study.

The role of fondaparinux in patients with NSTEMI was investigated in the OASIS-5 trial, a randomized, double-blind, noninferiority study of >20,000 patients who received fondaparinux 2.5 mg subcutaneously daily or enoxaparin 1 mg subcutaneously twice daily for a mean of 6 days.²⁷ Approximately 72% of patients underwent coronary angiography, 40% underwent PCI, and 15% underwent CABG surgery during or after hospitalization. Fondaparinux was judged to be noninferior to enoxaparin based on a similar rate of death, MI, or refractory ischemia after 9 days (5.8% with fondaparinux vs. 5.7% with enoxaparin). Fondaparinux was associated with significantly lower rates of major bleeding after 9 days (2.2% vs. 4.1% with enoxaparin, $P<0.001$) and death after 30 days ($P=0.02$) and 180 days ($P=0.05$) compared with enoxaparin. The practice of switching to UFH during coronary intervention in the enoxaparin group may partly explain the increased incidence of bleeding. Patients in the fondaparinux group were eligible to receive additional fondaparinux during the coronary intervention, but they did not receive UFH.

In OASIS-5 patients who underwent PCI, the incidence of catheter-related thrombi was significantly higher with the use of fondaparinux (0.9%) than with enoxaparin (0.4%, $P=0.001$).²⁷ This finding limits the use of fondaparinux in patients with NSTEMI because most of these patients in the United States undergo cardiac catheterization. Fondaparinux or enoxaparin is preferred over UFH for patients with NSTEMI or UA in whom cardiac catheterization is not planned.¹⁸ In the ACC/AHA guidelines for the management of UA or NSTEMI, the use of fondaparinux is preferred in patients at increased risk for

bleeding when a conservative approach is chosen.¹⁸ The use of fondaparinux in patients with NSTEMI or UA is not approved by the FDA, but it is endorsed by the ACC/AHA.^{16,18}

Therapies Specific to PCI

The use of PCI as the primary reperfusion strategy in patients with STEMI is associated with a significantly lower short-term mortality rate (5%) than the use of thrombolytic agents for reperfusion (7%, $P < 0.001$).²⁸ PCI carries a significantly lower risk of nonfatal reinfarction (3% vs. 7% with thrombolytic agents, $P < 0.001$) and stroke (1% vs. 2% with thrombolytic agents, $P < 0.001$).

Early invasive strategies have been compared with more conservative strategies in patients with NSTEMI or UA. In the TACTICS-TIMI 18 study of 2,220 patients with NSTEMI or UA, the rate of death, nonfatal MI, or rehospitalization for ACS at 6 months (the primary endpoint) was significantly lower with use of an early invasive strategy with cardiac catheterization within 4-48 hours and revascularization if needed (15.9%) than with use of a more conservative strategy of catheterization only for patients with evidence of recurrent ischemia or abnormal stress test results (19.4%, $P = 0.025$).²⁹ Troponin T levels were elevated in 54% of patients (i.e., 54% of enrollees had NSTEMI), and the benefit of the early invasive strategy was observed only in these patients. In patients without elevated troponin T levels (i.e., UA patients), there was no significant difference between the 2 interventions in the primary endpoint ($P = 0.46$).

Stent implantation after revascularization of a coronary artery covers the ruptured plaque and prevents it from coming in contact with constituents in the bloodstream that promote thrombosis. This approach obviates the need for prolonged anticoagulation. Nevertheless, the stent itself can act as a nidus for thrombosis; therefore, antiplatelet therapy is required to maintain patency of the reopened vessel.

Patients who undergo coronary intervention and stent implantation present a unique set of therapeutic challenges because of the need to balance the prevention of thrombosis with minimization of the risk of bleeding. A tremendous risk for clot formation exists when catheters, coronary wires, balloons, and stents are introduced into small coronary arteries. Introducing these devices into the femoral artery in the leg carries a potential for arterial injury and bleeding complications. Anticoagulants used during coronary interventions ideally have a rapid onset and a short half-life, can be easily monitored, and are associated with a low risk of bleeding.

Antiplatelet Therapies

Patients undergoing coronary stent deployment should receive aspirin 162 mg-325 mg preferably as a chewable, nonenteric formulation prior to the procedure.¹⁸ Aspirin 75 mg-325 mg per day should be continued indefinitely after stent insertion.

Platelet GP IIb/IIIa inhibitors are routinely used during PCI in patients with STEMI and NSTEMI.^{2,18} Their efficacy in reducing

the rate of death, MI, and the need for repeat revascularization is well established.³⁰ These agents increase the risk of thrombocytopenia and minor bleeding, but they do not increase the risk of major bleeding.³⁰

The need for a GP IIb/IIIa inhibitor in patients with NSTEMI or UA who receive loading doses of clopidogrel and aspirin before coronary intervention has been questioned. In the randomized, double-blind ISAR-REACT-2 trial of 2,022 patients with NSTEMI or UA, a 600-mg loading dose of clopidogrel was administered at least 2 hours prior to PCI.³¹ Patients were randomly assigned to receive abciximab plus UFH or placebo plus UFH. All patients received aspirin. After 30 days, the incidence of death, MI, or urgent target vessel revascularization (the primary endpoint) was 8.9% in the abciximab group and 11.9% in the placebo group ($P = 0.03$), representing a 25% reduction in risk of the primary endpoint with the use of abciximab. The benefit of abciximab was present even 12 months later.³² This difference was observed only in patients with elevated troponin levels (i.e., patients with NSTEMI instead of patients with UA). No significant differences were found between the 2 treatment groups in the risk of major bleeding, risk of minor bleeding, or need for transfusion. These findings provide support for the use of GP IIb/IIIa inhibitors in addition to aspirin and clopidogrel in patients with NSTEMI and elevated troponin levels or other high-risk features.¹⁸

Anticoagulant Therapies

The most commonly used anticoagulant during any coronary intervention remains UFH because it is easy to administer, has a short half-life, and its anticoagulant effects can be rapidly assessed using the ACT assay and readily reversed using protamine. In the cardiac catheterization laboratory, the track record for UFH is well established, and clinicians are familiar and comfortable with the agent.

Enoxaparin has not gained popularity as an anticoagulant agent for routine use during PCI because its anticoagulant effect cannot be readily monitored. Its half-life is relatively long, causing concern about the risk of bleeding during removal of devices from arteries after coronary intervention. Nevertheless, some patients with NSTEMI or UA who are initially treated with enoxaparin eventually undergo coronary intervention. The current ACC/AHA guidelines stipulate that if 8-12 hours have elapsed since the last subcutaneous dose of enoxaparin, an intravenous bolus dose of 0.3 mg per kg should be administered.^{2,18,33}

Experience from the OASIS-5 trial raised concerns about catheter-related thrombi in patients with NSTEMI or UA who received fondaparinux and underwent PCI.²⁷ Until more safety data become available, fondaparinux is unlikely to be widely used in the cardiac catheterization laboratory.

Another agent that has recently been evaluated is bivalirudin, a synthetic, reversible direct thrombin inhibitor that binds to circulating and clot-bound thrombin, preventing further steps in the coagulation process.³⁴ It has an immediate onset of action

after intravenous administration and a short half-life (25 minutes in patients with normal renal function).³⁵

Bivalirudin alone and in combination with a GP IIb/IIIa inhibitor were compared with heparin (UFH or enoxaparin) plus a GP IIb/IIIa inhibitor in the ACUTY study, a randomized, controlled, noninferiority study of more than 13,000 patients with NSTEMI scheduled to undergo angiography.³⁶ Most patients received clopidogrel. The 30-day incidence of death from any cause, MI, or unplanned revascularization for ischemia (i.e., ischemic outcomes) was 7.8% with bivalirudin alone, 7.7% with bivalirudin plus a GP IIb/IIIa inhibitor, and 7.3% with UFH or enoxaparin plus a GP IIb/IIIa inhibitor. The 30-day incidence of major bleeding with bivalirudin alone was significantly lower at 3% ($P < 0.001$) compared with a 5.3% bleeding rate in bivalirudin plus a GP IIb/IIIa inhibitor and a rate of 5.7% when using UFH or enoxaparin plus a GP IIb/IIIa inhibitor. The use of a liberal definition of major bleeding may have influenced these results. Nevertheless, bivalirudin alone may be chosen over bivalirudin plus a GP IIb/IIIa inhibitor and UFH or enoxaparin plus a GP IIb/IIIa inhibitor in patients with NSTEMI who undergo early invasive procedures because it is at least as effective for reducing ischemic outcomes with a lower risk for major bleeding.

About one half (56%) of ACUTY enrollees underwent PCI, and roughly two thirds of these patients received clopidogrel before PCI.³⁷ In patients with clopidogrel exposure before PCI, the 30-day incidence of ischemic outcomes was similar to bivalirudin alone (8.1%) and UFH or enoxaparin plus a GP IIb/IIIa inhibitor (8.4%). The 30-day rate of major bleeding was 3.6% and 7.2%, respectively. However, in patients without clopidogrel exposure before PCI, the incidence of ischemic outcomes was 9.6% with bivalirudin alone and 7.4% with UFH or enoxaparin plus a GP IIb/IIIa inhibitor. The 30-day rate of major bleeding in patients without clopidogrel exposure before PCI was 3.7% with bivalirudin alone and 5.5% with UFH or enoxaparin plus a GP IIb/IIIa inhibitor. These findings suggest that clopidogrel or a GP IIb/IIIa inhibitor is needed in patients with NSTEMI who undergo PCI; bivalirudin alone is inadequate.

■ Long-Term Antiplatelet Therapy After Coronary Stenting

A stent implanted in a coronary artery represents a foreign body in the prothrombotic milieu of the bloodstream of a patient recovering from ACS. In the early era of coronary stenting, the most feared complication was stent thrombosis, resulting in occlusion of the stent and potentially fatal MI.

Coronary stents are made of stainless steel or a cobalt-chromium alloy and are known as bare-metal stents. Dual antiplatelet therapy was provided for 30 days. After that time, a layer of endothelial cells of the native coronary artery had formed on the stent, preventing the stent from coming in contact with prothrombotic constituents in the bloodstream. The risk of stent thrombosis after 30 days decreased sufficiently to warrant therapy with aspirin alone.

Bare-metal stents were associated with an increased risk of restenosis due to the proliferation of smooth muscle cells in the arterial wall in response to injury caused by stent implantation. Drug-eluting stents were developed to minimize smooth muscle cell proliferation and prevent stent restenosis. These stents are coated with a polymer-eluting drug that inhibits cell proliferation. Drug-eluting stents have had a tremendous impact on the long-term efficacy of coronary interventions, and they have revolutionized interventional cardiology's management of patients with ACS, allowing the treatment of complex coronary artery blockages. The introduction of sirolimus- and paclitaxel-coated stents in 2003 and 2004, respectively, significantly reduced the risk of stent restenosis by up to 75% compared with approximately 10% for bare-metal stents.^{38,39} Members of a newer generation of drug-eluting stents (e.g., a zotarolimus-coated stent) possess anti-inflammatory, antimigratory, antiproliferative, or prohealing effects.^{40,41} However, one disadvantage is that the protective endothelial cell growth over the stent is also reduced, requiring longer dual antiplatelet therapy.

Risk of stent thrombosis is less than 1% within the first year after bare-metal stent implantation.⁴² In an analysis of safety data by the FDA, a small increase in stent thrombosis was found after 1 year in patients with drug-eluting stents compared with patients with bare-metal stents, but the increase was not associated with an increased risk for death or MI.⁴³

The ACC/AHA guidelines recommend aspirin 162 mg-325 mg per day for 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, followed by 75 mg-162 mg per day indefinitely in patients with all types of stents.^{2,18} After reviewing the safety of drug-eluting stents, an FDA panel recommended a 12-month course of dual antiplatelet therapy after drug-eluting stent implantation. In patients in whom there is concern about an increased risk for bleeding, a lower aspirin dosage (75 mg-162 mg per day) may be used during the initial period after stent implantation.² Clopidogrel 75 mg per day is recommended for at least 12 months after drug-eluting stent implantation unless the patient is at high risk for bleeding.^{2,18}

The risk of stent thrombosis after premature discontinuation of antiplatelet therapy is high and potentially catastrophic.⁴⁴ Discontinuation of clopidogrel, aspirin, or both due to adverse effects or plans to undergo surgery or invasive procedures (e.g., colonoscopy, biopsy) should be attempted only after consultation with a cardiologist.

■ Conclusions

The increasing complexity of the duration of treatment, dosages, and combinations of pharmacological agents available for management of ACS poses a challenge to clinicians when selecting appropriate antiplatelet and anticoagulant therapy. Although currently available, evidence-based guidelines are extremely helpful in directing treatment decisions, antiplatelet and anticoagulant

therapies must be selected based on an assessment of the risk for recurrent coronary events, death, and bleeding in a specific individual.

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Guidelines and Performance Measures for the Prevention and Treatment of Venous Thromboembolism

John Fanikos, RPh, MBA

ABSTRACT

BACKGROUND: Venous thromboembolism (VTE) is a common and often preventable cause of morbidity and mortality in the United States, with a widespread economic impact.

OBJECTIVE: To describe the prevalence, morbidity, mortality, and risk factors associated with VTE; adherence rates to evidence-based guidelines for VTE prophylaxis and treatment; efforts to raise awareness to address the VTE problem, including strategies to promote VTE prophylaxis; and the optimal treatment of VTE.

SUMMARY: An increased risk for VTE may be present in the early post-discharge period after brief hospitalization for medical and surgical patients. Adequate prophylaxis is the key to preventing VTE, recurrent VTE, post-thrombotic syndrome, and VTE-related death. Evaluation of clinical results indicates that there is considerable room for improvement in VTE prophylaxis use in hospitalized surgical and medical patients and in adherence to guidelines for VTE treatment. The heterogeneity of the patient population at risk for VTE is among the possible reasons for failure to institute pharmacologic or mechanical prophylaxis. National consensus standards for VTE prevention and treatment are applicable from hospitals to home care. Combinations of strategies are more effective than a single strategy in reducing VTE rates. In patients with VTE, the use of low-molecular-weight heparin facilitates early hospital discharge and outpatient treatment. Opportunities to minimize the hospital length of stay and costs by discharging patients with VTE while they are receiving overlapping parenteral and oral anticoagulation therapy are often missed.

CONCLUSIONS: Pharmacists' efforts to increase VTE awareness, ensure VTE prophylaxis, and recommend appropriate VTE treatment can have a favorable clinical and economic impact.

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Author

JOHN FANIKOS, RPh, MBA, is Assistant Director of Pharmacy at Brigham and Women's Hospital, Boston.

AUTHOR CORRESPONDENCE: John Fanikos, RPh, MBA, Assistant Director of Pharmacy, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115. Tel.: 617.732.7165; Fax: 617.566.2396; E-mail: jfanikos@partners.org

Deep vein thrombosis (DVT) develops in approximately 2 million Americans each year.¹ Most cases are asymptomatic; however, in approximately 600,000 cases, the thrombus embolizes and travels to the right atrium, through the right ventricle, and into the pulmonary arterial tree, lodging in the pulmonary vasculature. The mortality rate in patients with pulmonary embolism (PE) is high (approximately 10%), with nearly 60,000 deaths attributed to PE annually in the United States. Patients who survive PE may develop chronic pulmonary hypertension due to damage to the pulmonary vasculature. DVT can cause permanent damage to the valves of the venous system and may also result in post-thrombotic syndrome; chronic inflammation, edema, and pain; and, in severe cases, venous stasis ulcers of the lower extremities.

Prevalence

Venous thromboembolism (VTE) risk factors are common among hospitalized patients. Using criteria established by the American College of Chest Physicians (ACCP) in their evidence-based guidelines for the prevention of VTE, review of a U.S. database containing more than 38 million inpatient discharge records showed that more than 12 million (31%) patients met the ACCP criteria for prophylaxis: 4.3 million surgical and 7.7 million medical patients.^{2,3} The larger number of medical patients at risk for VTE is significant because, although VTE risk is well recognized in surgical patients, the danger for medical patients is frequently underappreciated.

While VTE is often considered to be a condition that develops primarily in elderly, bedridden hospital patients, recent medical record analysis provides a different picture.⁴ A review of 1,897 VTE sufferers from Worcester, Massachusetts, showed that 74% of these patients developed VTE signs and symptoms as outpatients. The mean age of those 1,399 outpatients who developed VTE was 63 years, and 33% were aged <55 years. In contrast, the mean age of the 498 inpatients who developed VTE was 67 years, with only 21% aged <55 years. The presence of 5 VTE risk factors (recent hospitalization, recent surgery, active malignant neoplasm, recent infection, history of VTE) was ascertained in outpatients who developed VTE: 30% had no risk factors, 32% had 1, and 34% had 2-3. For patients who experienced VTE within 3 months after hospitalization (with or without surgery), two thirds experienced VTE within 1 month. The median and mean length of stay for this initial hospitalization was 4.0 and 7.4 days, respectively. It appears that an increased risk for VTE is present in the early post-discharge period after brief hospital stays for both medical and surgical patients.

The risk of DVT without prophylaxis is 10%-20% in medical patients, 10%-80% for critical care patients, 20%-50% in patients

with stroke, and 40%-80% in patients with major trauma.² These rates are comparable with those in patients undergoing general or major urologic or gynecologic surgery or neurosurgery (15%-40%) or orthopedic surgery (40%-60%) who do not receive prophylaxis. The wide range in values depicts the asymptomatic nature of the disease and the low sensitivity of detection modalities.

■ VTE Awareness

Despite its prevalence and danger, VTE is a condition that frequently goes unrecognized by the general public. In 2002, the American Public Health Association sponsored a telephone survey of 1,003 American adults.⁵ The study population comprised 48% women, 52% men, 73% Caucasians, 12% African-Americans, 10% Hispanics, and 5% other races and ethnicities. Fifty percent had an education level consisting of a high school diploma or less. The survey demonstrated that 74% of respondents had little or no awareness of DVT. Of those who were aware of VTE, 57% were unable to name any common risk factors or conditions that predispose a person to DVT.⁵ Since 2002, several cases of VTE in public figures have helped to increase awareness. In 2003, David Bloom, an NBC journalist traveling with the U.S. Army 3rd Infantry Division in Iraq, died suddenly at the age of 39 from VTE. His widow, Melanie Bloom, has become active in educating the public about the dangers of DVT through media public service announcements as well as the Coalition to Prevent Deep-Vein Thrombosis (www.preventdvt.org). The latter is a group committed to educating the public, health care community, and policymakers about DVT and includes several pharmacy organizations, managed care providers, and physician groups. In addition, Bonnie Bernstein, a television sports journalist who survived DVT, will also appear in public service announcements as part of a DVT awareness campaign by the Coalition. Finally, Vice President Dick Cheney's travel-associated DVT in 2007 has also raised awareness of the seriousness of this condition.

■ Outreach Efforts

Recognition of VTE as a preventable event has led to various governmental outreach efforts. March was designated as DVT Awareness Month by the U.S. Senate in 2005, and the U.S. Surgeon General's Office is considering a Call to Action to address the problem. The Centers for Medicare and Medicaid Services and the Centers for Disease Control and Prevention initiated the Surgical Care Improvement Project (SCIP) in 2007 to improve surgical outcomes through reduction of post-operative complications.⁶ The goal of the SCIP is to reduce the incidence of surgical complications by 25% before the year 2010 by targeting adverse cardiac events, surgical site infections, post-operative pneumonia, and VTE.⁷ Specifically, the use of appropriate VTE prophylaxis within 24 hours before or after surgery and the diagnosis of DVT and PE within 30 days after surgery are used as SCIP measures of quality patient care.⁸

The National Quality Forum is collaborating with The Joint Commission to develop national consensus standards for VTE prevention and treatment.⁹ These standards provide a framework by which to identify preferred practices to ensure quality care for patients with or at risk for VTE. Performance measures are being developed to evaluate the quality of care provided to patients in screening for VTE risk, the institution of appropriate prophylaxis, and effective VTE treatment. These standards will be applicable from hospitals to home care. Draft candidate measures require appropriate overlap of parenteral and oral anticoagulation therapy, platelet count monitoring to detect heparin-induced thrombocytopenia (HIT), and justification for use of inferior vena cava filters instead of anticoagulation therapy, among various other aspects of VTE prevention, treatment, and outcomes.¹⁰ Public comments have been solicited, and the measures remain to be finalized.

Anticoagulation therapy is the cornerstone of VTE prophylaxis. The Joint Commission has recognized that anticoagulation therapy is a common cause of adverse drug events.¹¹ A Joint Commission National Patient Safety Goal for 2008 is to reduce the likelihood of patient harm associated with the use of anticoagulation therapy (warfarin, unfractionated, and low-molecular-weight heparin [LMWH], other anticoagulants).¹¹

■ VTE Risk

VTE risk factors (Table 1) involve stasis of the blood or changes in blood components or the endothelium that predispose patients to clot formation. A history of VTE is a particularly important risk factor.²

A retrospective review of the medical records of 1,000 randomly selected patients in 16 acute care hospitals in central Massachusetts evaluated the presence of 10 common risk factors (Table 1) among hospitalized patients. In this population, 78% of patients had 1 or more VTE risk factors, 48% had 2 or more VTE risk factors, 19% had 3 or more risk factors, 6% had 4 or more risk factors, and 1% had 5 or more risk factors.¹² The most common VTE risk factors were aged ≥ 40 years (59%), obesity (28%), and major surgery (23%).

The ACCP has defined 4 levels of risk for VTE in surgical patients based on age, type of surgery, presence of additional VTE risk factors, and incidence of DVT (especially proximal DVT involving clots found above the knee, which is particularly dangerous because of the high propensity to embolize), clinical PE, and fatal PE in untreated patients (Table 2).²

■ VTE Prophylaxis

The acute and long-term effects of VTE are largely preventable. Adequate prophylaxis is the key to preventing VTE, VTE recurrence, post-thrombotic syndrome, and VTE-related death. Various pharmacologic and mechanical interventions (graduated compression stockings [GCS], intermittent pneumatic compression [IPC]) may be used to reduce the risk of VTE.

TABLE 1 Risk Factors for VTE^a

Blood Stasis	Blood Component Changes	Endothelium Changes
Aged ≥40 years	Malignancy	Major surgery
Obesity	Estrogen use	Trauma
Cardiac dysfunction	Cancer therapy	Previous VTE
Cardiac dysfunction	Hypercoagulable conditions	Central venous catheter use
Stroke or paralysis	Nephrotic syndrome	Varicose veins
Prolonged immobility	Inflammatory bowel disease	Smoking
Respiratory failure		
Pregnancy		

^aCommon risk factors are in bold.^{2,12}

VTE=venous thromboembolism.

Anticoagulant therapy may be contraindicated due to a condition or surgery associated with a high risk of bleeding, a history of bleeding events (e.g., intracranial hemorrhage), or an allergy or adverse reaction to anticoagulant therapy. Mechanical prophylaxis is an option for these patients, and there is no risk of bleeding when these modalities are used. The weight of evidence is much greater with use of pharmacologic prophylaxis than with that supporting the efficacy of VTE prophylaxis with GCS and IPC. Mechanical prophylaxis is hindered by poor patient compliance, improper use, patient intolerance, and physical constraints from injuries (e.g., fractures, casts, dressings). The cost of IPC is high, and it is often not available after discharge.¹³ Despite these limitations, clinical trials in a variety of high-risk settings have shown that mechanical prophylaxis reduces the incidence of VTE.¹³ More importantly, when mechanical and pharmacologic strategies are combined, they may have synergistic effects.¹⁴⁻¹⁶ High-risk patients should be considered for combination methods.

Surgical Patients

ACCP-recommended prophylactic strategies for each level of VTE risk in surgical patients are listed in Table 2, with use of progressively more aggressive therapies as the degree of risk increases.² Use of LMWH is recommended instead of low-dose unfractionated heparin (LDUH) for patients undergoing orthopedic surgery or with trauma or spinal cord injury because LMWH is more effective than LDUH in preventing VTE.² However, patients undergoing general, gynecologic, or urologic surgery or neurosurgery may receive either LMWH or LDUH; both therapies are considered equally effective for prevention of VTE in these at-risk patient populations.²

A meta-analysis of 52 randomized controlled trials of VTE prophylaxis in 33,813 general surgery patients found that only

2% of patients discontinued prophylaxis because of bleeding complications.¹⁷ The percentage of patients receiving prophylaxis who required surgical intervention to control bleeding (0.7%) was no different from the percentage of control patients who required surgical intervention to control post-operative bleeding. Hence, concerns about bleeding should not deter clinicians from using low-dose anticoagulant prophylaxis in patients at risk for VTE.

Although aspirin is effective in reducing myocardial infarction, stroke, and thrombotic events on the arterial side of the circulatory system, it is not recommended for VTE prophylaxis.² The reduction in relative risk for DVT after general surgery that is associated with the use of aspirin is only 20%.¹⁸

Medical Patients

ACCP guidelines recommend the use of LDUH or LMWH in acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease or who have been confined to bed with 1 or more additional VTE risk factor.² A meta-analysis of 12 randomized controlled trials comparing the efficacy of subcutaneous LDUH (5,000 units) twice daily versus 3 times daily for VTE prophylaxis in 7,978 acutely ill medical patients found a significant risk reduction for proximal DVT and PE with 3 rather than 2 daily doses (0.9 vs. 2.3 events per 1,000 patient days, $P=0.05$). However, the use of LDUH 3 times daily was accompanied by a small but significant increase in risk for major bleeding (0.96 vs. 0.35 events per 1,000 patient days, $P<0.001$).¹⁹

Few studies have compared the efficacy of LDUH with LMWH for preventing VTE in medical patients. Most involved small numbers of patients and were conducted long ago using currently outmoded technologies to detect VTE. The PREVAIL study of VTE prevention in patients with hemiplegia after acute ischemic stroke is a contemporary trial. This patient population was studied because approximately 780,000 Americans experience stroke each year, and the incidence of DVT is approximately 50% within 2 weeks after hemiplegic stroke.^{20,21} The study examined 1,762 adults with acute ischemic stroke who were randomly assigned within 48 hours after symptom onset to receive LDUH (i.e., 5,000 units) subcutaneously every 12 hours or enoxaparin 40 mg subcutaneously every 24 hours for 10 days.²² Modern methods were used to detect DVT (bilateral contrast venography or ultrasonography) and PE (ventilation perfusion, helical computed tomographic scanning, or pulmonary angiography). The incidence of both VTE and DVT after 14 days was 18% with LDUH and 10% with enoxaparin, representing a significant 43% reduction in the relative risk for VTE and DVT with the use of enoxaparin versus LDUH ($P<0.001$ for both comparisons).²² The incidence of proximal DVT after 14 days was also significantly lower in the enoxaparin group (5%) compared with the LDUH group (10%, $P<0.001$), as well as the incidence of distal DVT after 14 days in the enoxaparin group (7%) compared with the LDUH group (13%, $P=0.001$). The 14-day incidence of PE was lower

TABLE 2 Risk of VTE and Prophylactic Strategies in Surgical Patients^a

Degree of Risk and Patient Characteristics	Calf DVT (%)	Proximal DVT (%)	Clinical PE (%)	Fatal PE (%)	Prophylactic Strategy
<i>Low</i> Minor surgery in patients aged <40 years with no additional risk factors	2	0.4	0.2	<0.01	Early and aggressive ambulation; no specific prophylaxis
<i>Moderate</i> Minor surgery in patients with additional risk factors, or surgery in patients aged 40-60 years with no additional risk factors	10-20	2-4	1-2	0.1-0.4	LDUH (5,000 units subcutaneously every 12 hours), LMWH, GCS, or IPC
<i>High</i> Surgery in patients aged 40-60 years with additional risk factors, or patients aged >60 years	20-40	4-8	2-4	0.4-1.0	LDUH (5,000 units subcutaneously every 8 hours), LMWH, or IPC
<i>Highest</i> Hip/knee arthroplasty, hip fracture surgery, major trauma, spinal cord injury, or surgery in patients aged ≥40 years with additional risk factors	40-80	10-20	4-10	0.2-5	LMWH, fondaparinux, warfarin (target INR 2.0-3.0), IPC or GCS + LDUH (5,000 units subcutaneously every 8 hours), or LMWH

^aFigures are the incidence of DVT or PE when prophylaxis is not used.²

DVT=deep vein thrombosis; GCS=graduated compression stockings; INR=international normalized ratio; IPC=intermittent pneumatic compression; LDUH=low-dose unfractionated heparin; LMWH=low-molecular-weight heparin; PE=pulmonary embolism; VTE=venous thromboembolism.

in the enoxaparin group (<1%) than in the LDUH group (1%), although the difference was not significant ($P=0.059$).

The incidence of bleeding at the end of treatment or within 48 hours after the end of treatment was identical (8%), and both groups had the same incidence of symptomatic intracranial hemorrhage (1%). The incidence of major extracranial hemorrhage was significantly higher in the enoxaparin group (1%) than in the LDUH group (0%, $P=0.015$), although the incidence of minor extracranial hemorrhage did not differ (5% enoxaparin, 6% LDUH; $P=0.50$). All-cause mortality at day 14 was 6% with enoxaparin and 5% with LDUH, constituting a difference that was not significant ($P=0.580$).

Thus, greater efficacy in preventing VTE can be achieved by using enoxaparin instead of LDUH. A post-hoc subgroup analysis revealed that the risk of VTE is reduced to a greater extent by enoxaparin than with LDUH in both men and women; in patients who began therapy 24-48 hours after symptom onset as well as in patients who began therapy less than 24 hours after symptom onset; in patients with and without diabetes, obesity, and a history of stroke; in patients with severe stroke as well as patients with less severe stroke; and in patients aged more than 75 years, aged 65-75 years, and aged less than 65 years. However, it is unclear whether the benefits of enoxaparin would be maintained if it had been compared with LDUH 5,000 units dosed every 8 hours rather than every 12 hours.

In the PRINCE trial, a randomized, open-label, parallel-group, noninferiority study of 451 patients with severe respiratory disease or heart failure, the incidence of thromboembolic events was 10.4% with LDUH subcutaneously 3 times daily and 8.4% with enoxaparin 40 mg subcutaneously once daily, a

difference that was not significant for the hypothesis, which indicated that enoxaparin is at least as effective as LDUH.²³ In the subset of 245 patients with severe respiratory disease, the incidence of thromboembolic events was similar with enoxaparin treatment (7.1%) and LDUH treatment (5.9%). In the subset of 206 patients with heart failure, the incidence of thromboembolic events was lower with enoxaparin (9.7%) than with LDUH (16.1%). However, no statistical difference was seen between the treatment groups. Enoxaparin was associated with significantly fewer injection site hematomas (7.2% vs. 12.6% with LDUH, $P=0.027$) and adverse events (46% vs. 54% with LDUH, $P=0.044$).¹⁸ No significant difference between treatment groups was found in the incidence of bleeding complications (1.5% with enoxaparin vs. 3.6% with LDUH). Once-daily administration of enoxaparin instead of 3-times-daily administration of LDUH contributed to the difference in the incidence of injection site hematomas, which could result in improved patient satisfaction.

Another noninferiority study of 148 patients with acute ischemic stroke found that the incidence of VTE was 19.7% with enoxaparin and 34.7% with LDUH 3 times daily, a difference that was significant ($P=0.044$).²⁴ The findings of these noninferiority studies suggest that the greater efficacy of enoxaparin compared with LDUH is evident primarily in patients at the highest risk for VTE (i.e., patients with heart failure or ischemic stroke), which supports the ACCP guidelines calling for LMWH but not LDUH in surgical patients at the highest risk for VTE based on a difference in efficacy.²

A meta-analysis of 36 randomized controlled trials of LDUH, LMWH, or both for VTE prevention in approximately 23,000

hospitalized medical patients found that LDUH 3 times daily is more effective in preventing DVT than LDUH twice daily.²⁵ Use of LMWH was associated with a significant 32% reduction in risk for DVT compared with LDUH ($P=0.004$).

The efficacy of extended-duration enoxaparin therapy for preventing VTE in medical patients was evaluated in the EXCLAIM trial, a randomized, double-blind, placebo-controlled study of 5,105 high-risk patients with acute medical illness and recent immobilization for up to 3 days.²⁶ Patients received enoxaparin 40 mg subcutaneously once daily for 10 ± 4 days followed by placebo or enoxaparin for an additional 28 ± 4 days. VTE incidence was 2.8% with extended-duration enoxaparin and 4.9% with placebo, representing a significant 44% reduction ($P=0.001$). The incidence of symptomatic VTE was also significantly reduced from 1.1% in the placebo group to 0.3% in the extended-duration enoxaparin group ($P=0.004$). Twelve (0.6%) patients receiving extended-duration enoxaparin and 3 (0.1%) patients receiving placebo experienced major bleeding ($P=0.019$), including 1 patient receiving extended-duration enoxaparin who died from a major bleeding event. There was no significant difference between treatment groups in 6-month all-cause mortality (10.1% with enoxaparin vs. 8.9% with placebo, $P=0.179$). These findings suggest a benefit from continuing enoxaparin after hospital discharge in at-risk, acutely ill medical patients; however, additional research is warranted to evaluate the risk for major bleeding.

HIT is an immune-mediated reaction to unfractionated heparin (UFH) or LMWH that leads to a precipitous drop in the platelet count and a hypercoagulable state, with an increased risk for thrombosis that can manifest as gangrene of the extremities. In 10,121 hospitalized medical patients who received LDUH 3 times daily or enoxaparin 40 mg once daily for VTE prophylaxis, the incidence of HIT was 0.51% and 0.08%, respectively ($P=0.037$).²⁷ The cost for hospitalization was significantly higher in patients with HIT (\$56,364) than in patients without HIT (\$15,231, $P<0.001$). When compared with UFH, LMWH prophylaxis incurs an incremental expense of approximately \$25 per day. When the costs of treating adverse events are included, LMWH prophylaxis in hospitalized medical patients is associated with a cost savings of \$13.88 per patient.

Several considerations might enter into the choice between LDUH and LMWH for an acutely ill medical patient at risk for VTE. The lower acquisition cost and reduced major bleeding risk support LDUH use.²³ The lower risk of minor bleeding and HIT, greater patient acceptance, and savings in nursing time for drug administration support the use of LMWH.^{23,27}

Guideline Adherence

A variety of reasons may contribute to failure to use VTE prophylaxis or improper prophylaxis, including the heterogeneity of the patient population at risk and the fact that prevention and treatment of VTE does not fall under the purview of any one

specialty practitioner. Some practitioners appear to underappreciate the risk of VTE and its dangers, and assessing VTE risk may be perceived as an unnecessary burden.

Data from U.S. and international registries reveal that only a minority of hospital patients with acute medical illness receive VTE prophylaxis, and differences exist in the strategies employed.²⁸⁻³¹ The IMPROVE Registry found IPC to be the most common VTE prophylaxis strategy used in the United States. For pharmacologic prophylaxis, UFH was the most commonly employed in the United States, whereas LMWH prophylaxis was more common outside the United States.

The rate of adherence to ACCP guidelines for the prevention of VTE in hospitalized patients with trauma, acute spinal cord injury, or medical conditions that place them at increased risk (e.g., acute myocardial infarction, ischemic stroke, cancer, heart failure, severe lung disease) as well as in patients undergoing major orthopedic, general, gynecologic, or urologic surgery or neurosurgery was assessed in a retrospective study.³² The overall guidance adherence rate was 13%: 7% in gynecologic surgery, 10% in urologic surgery, 13% in general surgery, 52% in orthopedic surgery, and 5% in patients with medical conditions that place them at risk. Failure to use prophylaxis of any kind when warranted was a common cause for nonadherence to ACCP guidelines, affecting more than one half of the patients regardless of the type of surgery or medical condition. In some patients, nonadherence was also attributed to inadequate duration of prophylaxis due to therapy starting late, ending early, or both. These findings suggest considerable room for improvement in the use of VTE prophylaxis in hospitalized surgical and medical patients. They also suggest a role for pharmacists to devote efforts to ensuring that prophylaxis is used when warranted and that therapy starting and ending times are appropriate.

In a separate analysis of data from nearly 200,000 hospitalized medical patients at risk for VTE, the rate of VTE prophylaxis was 62%, and the rate of appropriate prophylaxis in accordance with ACCP guidelines was 34%.³³ Results were similar when patients were stratified by disease or condition (myocardial infarction, heart failure, stroke, trauma, cancer, lung disease, spinal cord injury). These findings are consistent with the observations of other investigators.^{34,35}

In a study of 227 hospitalized medical patients, 153 patients had at least 1 VTE risk factor.³⁶ Prophylaxis was not provided to 52 (34%) of these at-risk patients. In the other 101 at-risk patients, prophylaxis was continued until hospital discharge in only 33 (22%) at-risk patients.

In an historical cohort study of 253 cases of VTE diagnosed at a large teaching hospital, 179 (71%) were spontaneous, 44 (17%) were preventable, 21 (8%) were nonpreventable, and 9 (4%) were ineligible for prophylaxis.³⁷ In the 44 preventable cases, prophylaxis was omitted in 21 (48%), the duration of prophylaxis was inadequate in 10 (23%), and the remainder involved the wrong type of prophylaxis, delay in initiation of prophylaxis, or

inadequate dose or dosing frequency. These findings suggest that opportunities to prevent VTE often are missed in hospitalized medical patients.

In a subgroup analysis of data from a prospective registry of 5,451 patients with DVT at 183 American hospitals, the incidence of PE was significantly higher in medical patients with DVT (22.2%) than in surgical patients with DVT (15.5%, $P < 0.001$).³⁸ The use of VTE prophylaxis was significantly lower in medical (25%) than in surgical patients with DVT (54%, $P < 0.001$). These findings underscore the need for efforts to ensure the use of VTE prophylaxis in medical patients.

The presence of some VTE risk factors is not always immediately apparent. The complexity of dosing and therapeutic monitoring for anticoagulants may be daunting. A clinician's concerns about anticoagulant-related hemorrhagic complications may pose a barrier to prophylaxis use. A survey of surgeons found that, although 73% stated that they perform risk stratification, a detailed analysis of prescribing practices failed to confirm this. Furthermore, more than one half of these surgeons recalled a complication of their preferred prophylaxis strategy.³⁹ A survey of hospital pharmacists showed that only 59.8% of hospitals had programs that encouraged VTE prophylaxis.⁴⁰ Opportunities exist for pharmacists to improve the bedside delivery of VTE prophylaxis as well as implement performance improvement programs.

Strategies to Improve VTE Prophylaxis

Various approaches have been used to promote VTE prophylaxis including risk assessment scoring systems, risk recognition systems, and prophylaxis default systems. Risk assessment scoring systems provide a tool not only to identify patients in whom prophylaxis is warranted, but also to determine the type of prophylaxis to use. Many such scoring systems are incorporated into order forms or computerized physician order-entry systems. A weighted point value is assigned to VTE risk factors, a total score is calculated manually or automatically, and a prophylactic intervention is recommended based on the total score, usually in accordance with ACCP guidelines.^{41,42} Risk recognition systems involve the identification of comorbid conditions and other factors that increase the risk for VTE without determining a score to quantify the risk for VTE. One such system involves the use of a flow diagram to identify patients at risk for VTE because of acute medical illness or other risk factors and to determine whether pharmacologic or nonpharmacologic prophylaxis is indicated.⁴³ Prophylaxis default systems involve the use of automatic orders for VTE prophylaxis. Orders are discontinued by the physician for patients who are not at risk for VTE.

The efficacy of an intervention to improve VTE prophylaxis rates in 5,500 medical patients was evaluated in a tertiary care university teaching hospital.⁴⁴ The intervention involved the use of a patient history form containing a scheme for assessing and documenting risk for VTE at the time of admission, an admission

order set with recommendations for optimal VTE prophylactic regimens, and educational sessions for house staff and clinical pharmacists. In high-risk patients, the prophylaxis rate was 43% before the intervention and 72% after the intervention. In lower-risk patients, prophylaxis improved from 31% to 64%.

At a community teaching hospital, clinical pharmacists developed an education program focused on the importance of providing VTE prophylaxis to medically ill patients.⁴⁵ The program involved in-service education, newsletters, and quality assurance presentations. Retrospective data from 344 patients before the intervention were compared with data from 297 patients after the intervention. The use of VTE prophylaxis increased significantly from 43% before the intervention to 58% after the intervention ($P < 0.001$). Significant increases also were observed in the use of suitable prophylaxis (LDUH 2-3 times daily or LMWH) from 38% before the intervention to 49% after the intervention ($P = 0.006$) as well as the use of optimal prophylaxis (LDUH 3 times daily or LMWH) from 11% to 44% ($P < 0.001$).

In 13 tertiary care teaching hospital medical wards, a practice guideline defining patients at risk for VTE and appropriate prophylaxis was implemented in conjunction with the use of educational presentations, printed educational materials, and feedback to providers.⁴⁶ In the pre-intervention period, 18% of clinicians required recommendations to prescribe appropriate prophylaxis, whereas in the post-intervention period, only 7% required similar directives. The incidence of DVT decreased from 9.5% in the pre-intervention period to 3.2% in the post-intervention period ($P < 0.01$).

The impact of a computer-alert program designed to encourage VTE prophylaxis on the incidence of DVT was evaluated in a randomized controlled trial of 2,506 high-risk patients at a tertiary care teaching hospital.⁴⁷ The computer-alert program calculated a VTE risk score and sent an electronic alert to physicians if a patient's score exceeded an established threshold of 4 or more risk-score points. The alert provided the score as well as an electronic link to VTE prevention guidelines and facilitated computerized entry of prophylaxis orders. Alerts were not sent to physicians of patients randomly assigned to the control group. The use of VTE prophylaxis was significantly higher in the intervention group (34%) than in the control group (15%, $P < 0.001$). The incidence of VTE after 90 days was significantly lower in the intervention group (4.9%) than in the control group (8.2%, $P < 0.001$). There was no significant difference between the 2 groups in the incidence of major hemorrhage after 30 days (1.5% in both groups, $P = 0.87$).

A systematic review of 30 intervention studies designed to improve VTE prophylaxis rates revealed that combinations of strategies were more effective than a single strategy.⁴⁸ Systems for reminding clinicians to assess patients for VTE risk, electronic decision-support systems or paper-based reminders, and audit and feedback were the most effective strategies.

■ VTE Treatment

According to ACCP guidelines, VTE may be treated using weight-based dosing of intravenous UFH to achieve an activated partial thromboplastin time (aPTT) within the therapeutic range established by the laboratory performing the assay, with dosage adjustments made using a standardized nomogram.⁴⁹ The use of subcutaneous LMWH once or twice daily is an alternative that facilitates early hospital discharge and subsequent outpatient treatment.⁴⁹

Triage of VTE patients from the emergency department and primary care provider offices has further facilitated care in the ambulatory care setting without compromising therapy effectiveness or patient safety.⁵⁰ Reduction in LMWH dosage is recommended if LMWH is used in patients with severe renal impairment;⁵¹ however, intravenous UFH is preferred over LMWH therapy for such patients.⁴⁹ Warfarin therapy should be initiated at the same time as UFH or LMWH in patients with VTE;⁴⁹ the therapies should overlap by at least 5 days. UFH or LMWH should be discontinued when the international normalized ratio (INR) is stable and exceeds 2.0.⁴⁹

In a randomized study of 500 patients with acute proximal DVT who were randomly assigned to receive standard intravenous UFH or enoxaparin 1 mg per kg subcutaneously twice daily, there was no significant difference in the rate of recurrent VTE (6.7% vs. 5.3%, respectively; $P=0.570$) or major bleeding (1.2% vs. 2.0%, respectively; $P=0.500$).⁵² The mean duration of hospital stay was 6.5 days in the UFH group and 1.1 days in the enoxaparin group.

Fixed-dose, weight-adjusted subcutaneous UFH therapy without dose adjustment based on aPTT values may be used for VTE treatment, with the potential for substantial cost savings. This therapy was compared with LMWH in the FIDO study, a randomized, open-label, noninferiority trial of 708 patients with acute VTE.⁵³ Patients assigned to the UFH group received a 333-units-per-kg subcutaneous dose followed by 250 units per kg subcutaneously every 12 hours. Patients assigned to the LMWH group received enoxaparin or dalteparin 100 units per kg subcutaneously every 12 hours (the choice of LMWH depended on local availability). Both treatments were given for at least 5 days on an inpatient or outpatient basis. Warfarin was initiated on the same day as UFH and LMWH in most cases, and warfarin was continued for at least 3 months, with doses adjusted to achieve an INR of 2.0-3.0.

In the FIDO study, treatment was administered on an outpatient basis in 72% of patients in the UFH group and 68% of patients in the LMWH group.⁵³ No significant difference between treatment groups was found in the incidence of recurrent VTE after 3 months (3.8% with UFH, 3.4% with LMWH; $P=0.002$). Incidence of major bleeding within 10 days was similar in the UFH (1.1%) and LMWH groups (1.4%). Blinded aPTT values were obtained on the third day of UFH therapy due to concerns that low values might be associated with recurrent VTE and high

values might be associated with bleeding during fixed-dose UFH therapy, but no such associations were found in the UFH group. Although the number of patients enrolled in this study was small, fixed-dose, weight-adjusted subcutaneous UFH, without routine aPTT monitoring, appears as safe and effective as LMWH for the treatment of acute VTE.

Fondaparinux, a subcutaneously delivered antithrombotic agent that inhibits activated coagulation factor X, was not approved by the U.S. Food and Drug Administration (FDA) at the time that the ACCP guidelines for VTE treatment were released. The FDA has since approved the drug for treatment of acute DVT and PE.⁵⁴ Fondaparinux was compared with intravenous UFH and enoxaparin in randomized, controlled, noninferiority studies of patients with acute symptomatic DVT or PE.⁵⁵⁻⁵⁶ In an open-label trial, 2,213 patients with acute symptomatic PE were randomly assigned to receive UFH by continuous intravenous infusion, with the aPTT at 1.5-2.5 times a control value, or by single daily subcutaneous doses of fondaparinux 5.0 mg, 7.5 mg, or 10.0 mg for patients weighing less than 50 kg, 50 kg-100 kg, or more than 100 kg, respectively.⁵⁵ Both treatments were continued for at least 5 days until an INR >2.0 was achieved with warfarin therapy. No significant difference between treatment groups was found in the incidence of recurrent VTE (5.0% with UFH, 3.8% with fondaparinux). Incidence of major bleeding was also similar in the 2 treatment groups (1.1% with UFH, 1.3% with fondaparinux). Fondaparinux was at least as safe and effective as adjusted-dose intravenous UFH for the treatment of acute symptomatic PE.

In a randomized, double-blind study, 2,205 patients with acute symptomatic DVT were randomly assigned to receive enoxaparin 1 mg per kg subcutaneously twice daily or single daily subcutaneous doses of fondaparinux, as described in the previous paragraph.⁵⁶ Both treatments were continued for at least 5 days until an INR >2.0 was achieved with warfarin therapy. No significant difference between treatment groups was found in the incidence of recurrent VTE (4.1% with enoxaparin, 3.9% with fondaparinux). Incidence of major bleeding was also similar in the 2 treatment groups (1.2% with enoxaparin, 1.1% with fondaparinux). Fondaparinux was at least as safe and effective as weight-based enoxaparin for the treatment of acute symptomatic DVT.

Most outpatient VTE treatment protocols call for daily monitoring of the INR with a target value of 2.5 and a therapeutic range of 2.0-3.0.⁴⁹ In patients receiving UFH or LMWH, platelet counts typically are measured on days 3-7 of treatment to detect HIT. At Brigham and Women's Hospital in Boston, outpatients receiving treatment for VTE are monitored using daily telephone calls by nurses and pharmacists. Physician follow-up is conducted through clinic visits scheduled 1 week after hospital discharge and then as needed to ensure thrombus resolution and appropriate patient outcomes.

The appropriateness of anticoagulant therapy for VTE was evaluated in a retrospective review of data from medical records

of 939 inpatients at 38 U.S. hospitals.³⁵ Overlap of parenteral and oral anticoagulant therapies was appropriate in 246 (51%) of the 486 patients who received overlapping therapies. Most patients were not discharged from the hospital until after parenteral therapy was discontinued. A total of 241 (27%) patients were discharged receiving bridge (both parenteral and oral) anticoagulation therapy. The mean length of stay was significantly shorter in patients discharged receiving bridge therapy compared with patients discharged receiving warfarin alone after discontinuation of parenteral anticoagulation therapy in the hospital (4.0 vs. 8.1 days, $P < 0.001$). These findings suggest that there is room for improvement in adherence to ACCP recommendations for overlap of anticoagulation therapy, and opportunities to minimize the hospital length of stay and costs by discharging patients while they are receiving bridge therapy often are missed.

ACCP guidelines address the duration of warfarin therapy in patients with VTE.⁴⁹ In patients with VTE caused by a risk factor that is reversible or transient (e.g., associated with surgery), 3 months of warfarin therapy are recommended. At least 6-12 months of warfarin therapy are recommended for patients with a first episode of idiopathic VTE, and indefinite therapy should be considered for such patients. Anticoagulation treatment for an indefinite period is recommended for patients with 2 or more VTE episodes and for patients with a first episode of VTE and cancer or certain inherited causes of thrombophilia.

On the other hand, there are potential alternatives to long-term warfarin treatment. Long-term LMWH (tinzaparin) therapy was compared with usual care involving intravenous or subcutaneous UFH and warfarin therapy in a randomized, open-label study of 737 patients with proximal DVT.⁵⁷ No significant difference between treatment groups was found in the incidence of VTE recurrence after 3 months (4.9% with LMWH, 5.7% with usual care) or at 12 months (8.9% with LMWH, 9.8% with usual care). Incidence of bleeding was significantly lower with LMWH (13.0%) than with usual care (19.8%, $P = 0.011$), which was largely due to less minor bleeding. These findings suggest that LMWH may be used as safely and effectively as warfarin on a long-term basis.

In summary, LMWH, fondaparinux, and subcutaneous UFH represent effective alternatives to intravenous UFH for acute VTE treatment and can be administered safely either in the hospital or on an outpatient basis. In addition, these agents represent alternatives to oral warfarin for long-term prevention of recurrent VTE events.

Conclusions

VTE is a major clinical problem with significant financial implications, yet awareness is limited both in the general public and also, to some extent, in the medical profession. Despite the existence of considerable research evidence and the publication of specific guidelines for VTE prophylaxis, these measures are often not implemented. When VTE strikes, treatment options now extend

beyond the hospital walls and should be considered to avoid or abbreviate hospital stays. Pharmacists can play an important role in increasing awareness of the morbidity and mortality associated with VTE, improving the identification of patients at risk for VTE, increasing adherence to evidence-based guidelines for VTE prevention, and enhancing treatment to optimize outcomes. Efforts to improve VTE prophylaxis and treatment should not focus on hospitals alone, but should also be applied to patients in long-term care facilities, to home care patients, and to outpatients.

DISCLOSURES

John Fanikos is both a consultant to and on the Speakers Bureau of Eisai, GlaxoSmithKline, sanofi-aventis/Bristol-Myers Squibb, and The Medicines Company. Fanikos is also on the Speakers Bureau of Genentech, Inc. and Schering. Fanikos was responsible for the entire study concept and design of this article. He performed all of the data collection, data interpretation, writing, and revision of this article.

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Management of Acute Coronary Syndrome and Venous Thromboembolism: A Managed Care Perspective

Randall D. Seifert, PharmD

ABSTRACT

BACKGROUND: Acute coronary syndrome (ACS) and venous thromboembolism (VTE) are costly conditions, largely due to the high initial cost of treatment, patient nonadherence to prescribed antiplatelet therapy, avoidable rehospitalization in patients with ACS, and high rate of recurrence and long-term complications in patients with VTE.

OBJECTIVES: To discuss the economic impact of ACS and VTE; factors that contribute to preventable morbidity, mortality, and costs associated with these conditions; and strategies that managed care pharmacists can use to improve clinician knowledge of evidence-based treatment guidelines and patient adherence to the treatment plan, thereby improving clinical and economic outcomes.

SUMMARY: Premature discontinuation of antiplatelet therapy increases the risk of death and rehospitalization in patients with ACS. Factors associated with premature discontinuation include advanced age, lack of education, unmarried status, pre-existing cardiovascular disease, high cost of health care, failure to receive discharge instructions, and lack of referral for cardiac rehabilitation. Managed care plan benefit design should provide for the effective treatment of ACS and VTE by identifying the optimal type and duration of anticoagulant and antiplatelet therapy. In patients with VTE, the use of low-molecular-weight heparin (LMWH) in outpatients is as safe and effective and less costly than standard intravenous unfractionated heparin on an inpatient basis. Long-term LMWH treatment for acute deep vein thrombosis is safe and effective, and it is preferred over warfarin for patients with cancer. Managed care pharmacists can improve the quality of care for patients with ACS and VTE by using a variety of strategies to improve clinician knowledge of evidence-based treatment guidelines and patient adherence to the treatment plan.

CONCLUSIONS: Efforts by managed care pharmacists to improve the quality of care for patients with ACS and VTE can improve patient outcomes and reduce health care utilization and costs.

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Author

RANDALL D. SEIFERT, PharmD, is Senior Associate Dean at the University of Minnesota, Duluth.

AUTHOR CORRESPONDENCE: Randall D. Seifert, PharmD, Senior Associate Dean, University of Minnesota, Duluth, 232 Life Sciences, 1110 Kirby Dr., Duluth, MN 55812. Tel.: 218.726.6032; Fax: 218.726.6500; E-mail: rseifert@umn.edu

Acute coronary syndrome (ACS) and venous thromboembolism (VTE) place a large economic burden on society. The invasive cardiovascular procedures or intensive medical management that is required for patients with ACS and VTE can be costly due to the recurrence of deep vein thrombosis (DVT). Treatment and management of these conditions via practice guidelines can be challenging and controversial. Balancing cost with appropriate therapy is sometimes difficult to achieve.

Acute Coronary Syndrome Cost Implications

ACS is a manifestation of coronary heart disease (CHD). In 2008, the estimated cost of CHD in the United States is \$156.4 billion, including \$87.6 billion for direct costs and \$68.8 billion for indirect costs.¹

The scope of the problem for managed care organizations is significant as revealed in a retrospective analysis of claims for 13,731 managed care patients with a new onset of ACS. This well-designed study revealed that the average total cost during the first year after diagnosis was \$22,529 (mean: 9.75 months of follow-up), with 71% of these costs attributable to hospitalizations.² More than one rehospitalization after the index event was required for 3,641 (26.5%) of the 13,731 patients, thereby contributing significantly to the overall cost.²

In another retrospective study of claims for 16,321 managed care patients hospitalized for ACS, 21% of patients were rehospitalized for ischemic heart disease during a 1-year follow-up period at an average cost of \$28,637.³ Nearly one-half of the patients (46%) underwent a revascularization procedure during the initial hospitalization. In the year after the index hospitalization, 90% of patients received lipid-lowering, antihypertensive, or antiarrhythmic medications, and 50% of patients received antiplatelet or anticoagulant medications.

Similarly, in a database of 3,258 managed care patients with ACS who underwent percutaneous coronary intervention, the rate of rehospitalization for restenosis was 12.5%.⁴ The mean cost over a 1-year period for rehospitalized patients was \$31,954, and the incremental cost for each patient with repeat revascularization was \$24,955.

Clinical Outcomes

Long-term use of dual antiplatelet therapy with aspirin and the thienopyridine clopidogrel is recommended for 12 months in patients with ACS, particularly in patients with drug-eluting coronary stents (see the article by Sobieszczyk in this supplement).^{5,6} The causes and impact of patient nonadherence to prescribed antiplatelet therapy were evaluated in a prospective observational study of 500 patients with ACS and drug-eluting stents who received a prescription for thienopyridine therapy

at the time of hospital discharge.⁷ Thirty days after discharge, 68 (13.6%) patients had stopped taking the thienopyridine. The all-cause mortality rate within 1 year after discharge was significantly higher in patients who stopped thienopyridine therapy prematurely (7.5%) than in those who continued therapy beyond 30 days (0.7%, $P<0.001$). The number of patients needed to treat beyond 30 days with a thienopyridine to prevent 1 death is 15 patients. The rate of rehospitalization was also higher in patients who stopped thienopyridine therapy early (23%) than it was in those who continued therapy (14%, $P=0.08$). This result was not statistically significant and was likely related to the study methods; however, the absolute risk reduction of 9% (number needed to treat=11) does shed light on some possible issues related to poor patient adherence and resultant clinical outcomes. These findings appear to underscore the preventable nature of rehospitalization and death and the importance of long-term antiplatelet therapy in patients with ACS and drug-eluting stents.

Compared with patients who continued thienopyridine therapy for at least 30 days, patients who discontinued therapy earlier were significantly older (64 years vs. 60 years, $P=0.03$), less likely to have a high school education (73% vs. 89%, $P<0.001$) and be married (56% vs. 71%, $P=0.01$), and more likely to have pre-existing cardiovascular illnesses (49% vs. 30%, $P=0.003$) and avoid health care due to cost (24% vs. 13%, $P=0.02$).⁷ Patients who discontinued therapy prematurely were also less likely to have received discharge instructions (88% vs. 95%, $P=0.05$) or a referral for cardiac rehabilitation (50% vs. 64%, $P=0.03$) than patients who continued therapy. These findings have important implications regarding the identification of patients with ACS so as to counsel them about the importance of adhering to prescribed antiplatelet therapy on a long-term basis to prevent death and costly hospitalizations.

■ Venous Thromboembolism

Cost Implications

Venous thromboembolism—DVT and pulmonary embolism (PE)—is costly because of the high rate of DVT recurrence (8%-17% within 2 years) and the costs associated with long-term sequelae, particularly post-thrombotic syndrome (see the article by Fanikos in this supplement).^{8,9} In a retrospective pharmacoeconomic analysis, extrapolation of data from patient and administrative records for managed care patients with acute proximal DVT suggests that the annual costs of treatment in 1997 amounted to \$1.5 billion in the United States.¹⁰

A more comprehensive, controlled, retrospective observational study was conducted of administrative claims data for 26,958 managed care patients with DVT, PE, or both and patients with possible post-thrombotic syndrome.¹¹ The mean annualized total health care costs for DVT, PE, or both were \$33,200, \$31,300, and \$38,300, respectively, compared with \$2,800 for matched control patients. The mean annualized total health care costs were \$47,600 in patients with post-thrombotic syndrome and

\$35,900 in patients without the syndrome (i.e., the incremental cost of post-thrombotic syndrome was \$11,700).

Clinical Outcomes

Several issues related to the optimal use of anticoagulant agents for the treatment of VTE have been raised. Quality improvement efforts by managed care pharmacists should address these issues.

The feasibility, safety, and efficacy of subcutaneous low-molecular-weight heparin (LMWH) therapy in outpatients instead of standard intravenous unfractionated heparin (UFH) in inpatients has been demonstrated in randomized, controlled, and prospective cohort studies of patients with DVT, PE, or both, although fewer data are available on the use of LMWH in the treatment of PE than of DVT.¹²⁻¹⁵ Pregnancy, a history of VTE, a high likelihood of patient noncompliance, and the presence of thrombophilic or serious comorbid conditions were among exclusion criteria in these studies. Nevertheless, most patients with clinically stable VTE are candidates for outpatient LMWH therapy.

Low rates of DVT recurrence (3%-7%) and bleeding (3%-4%) were observed in cost-effectiveness studies of LMWH for the treatment of DVT.^{16,17} The acquisition cost is higher for LMWH than for UFH. Cost savings, primarily from a shortened length of hospital stay, were associated with the use of LMWH instead of UFH in a study of 300 patients with DVT.¹⁶ In another cost-effectiveness analysis, the cost of initial care was higher in patients treated with LMWH than in patients treated with UFH, but this higher initial cost was partly offset by lower costs for early complications.¹⁷

In a prospective study of an outpatient DVT treatment protocol at a staff model health maintenance organization, 102 (61%) of 167 patients with VTE were eligible for and received LMWH therapy as outpatients.¹⁸ Their VTE recurrence rate was 1.9% versus 4.1% in a cohort of patients treated previously with UFH as inpatients. None of the outpatients or inpatients experienced major bleeding. The average length of hospital stay was 0.79 days for outpatients compared with 5.3 days for inpatients. Total costs for outpatients (\$229,270) were roughly one half as much as for inpatients (\$484,288). The overall outpatient care experience was rated very good or excellent by 41 (84%) of 49 outpatients due to avoidance of hospitalization, less disruption in routine, and a quick return to work. The potential for cost savings and patient satisfaction without compromising efficacy or safety associated with the use of LMWH on an outpatient basis for treatment of patients with VTE should be considered in designing managed care benefits. Additional randomized controlled trials are needed to support the potential benefits of LMWH in outpatients for the treatment of clinically stable PE.

■ Managed Care Plan Benefit Design

Managed care plan benefits should include provisions for the optimal duration of therapy with anticoagulants for the

prevention and treatment of VTE. Three months of treatment with a vitamin K antagonist (e.g., warfarin) are recommended by the American College of Chest Physicians for patients with a first episode of VTE due to a transient, reversible cause because a shorter duration of therapy (4-6 weeks) is associated with an increased risk for VTE recurrence.¹⁹⁻²² At least 6-12 months of anticoagulant treatment are recommended for an idiopathic first DVT episode, and treatment for an indefinite period is recommended for patients with 2 or more VTE episodes and for patients with a first episode of VTE and cancer or certain inherited causes of thrombophilia (see the article by Fanikos in this supplement).¹⁹

In patients with acute DVT, treatment with LMWH for 3-6 months is at least as effective in preventing recurrent DVT as a vitamin K antagonist with doses adjusted to maintain an international normalized ratio (INR) of 2.0-3.0, and LMWH therapy is associated with a lower risk for minor bleeding.²³⁻²⁵ In a randomized, open-label study of 672 patients with cancer and acute DVT, 6 months of treatment with the LMWH dalteparin 200 units per kg subcutaneously once daily for 1 month followed by 150 units per kg subcutaneously once daily for 5 months was compared with dalteparin 200 units per kg subcutaneously once daily for 5-7 days followed by a vitamin K antagonist with the dose adjusted to maintain an INR of 2.5 for 6 months.²⁵ The probability of DVT recurrence after 6 months was 9% in the dalteparin-only group and 17% in the dalteparin-vitamin K antagonist group, providing a difference that is significant ($P=0.002$). The incidence of major bleeding was not significantly different at 6% and 4%, respectively ($P=0.27$). The number of patients needed to treat with dalteparin only for 6 months to prevent 1 case of DVT recurrence is 13. Thus, long-term LMWH treatment for acute DVT is safe and effective and is preferred over warfarin for patients with cancer.

■ Opportunities for Managed Care Pharmacists

Evidence-based guidelines provide a framework for managed care interventions and quality improvement efforts. Recently updated guidelines for the management of ACS are available from the American College of Cardiology and American Heart Association.^{5,6} Managed care pharmacists can familiarize themselves with guidelines for ACS and VTE as well as other recent research findings related to the management of these conditions by using Web-based educational programs available from ASHP Advantage (www.ashpadvantage.com/clot/).

Incorporating new guidelines and ensuring adherence to the guidelines in managed care can be a challenge without making major changes to the chronic care delivery model. Advances in information technology can facilitate the incorporation of and promote adherence to new treatment guidelines. Research involving evaluation of managed care operations is needed to identify strategies to improve clinician knowledge of and adherence to treatment guidelines and patient adherence to prescribed therapy. Patient-centered management approaches,

disease management programs that promote medication adherence, and pharmacist-based medication therapy management with reconciliation between the inpatient and outpatient settings are possible strategies to achieve these goals.

One such strategy was outlined in the Asheville Project, which is a patient-centered management model for improving medication adherence in patients with chronic conditions (e.g., diabetes, asthma, hypertension, dyslipidemia) that, in theory, could be applied to patients with ACS or VTE.²⁶ Improved patient outcomes and substantial reductions in health care utilization, sick days, and costs have been realized using this model. The pharmacist serves as a health coach by directing the patient to health information and monitoring drug therapy.

In addition, Health Effectiveness Data Information Set (HEDIS) criteria are used by most managed care plans to measure health care quality. Only 1 HEDIS criterion—beta-blocker use after acute myocardial infarction—relates directly to patients with ACS, and none pertain to VTE prevention or treatment.²⁷ Other HEDIS criteria address the management of diabetes mellitus complicated by high cholesterol and high blood pressure, which are CHD risk factors.

Implementing new quality measures with pay-for-performance financial incentives is another approach that managed care pharmacists can use to improve the quality of care for patients with ACS or VTE. A reduction in health care costs could be realized. Modifying the managed care plan benefit structure to reduce premiums or copayments for medications is a possible approach to promote program participation and adherence to prescribed therapy by patients.

This review found several good-quality studies that are relevant to managed care pharmacy practice; however, there is a need to initiate studies that document best practice interventions, whether they are clinical or related to benefit design. The need to identify and implement strategies to improve clinician adherence to treatment guidelines and patient adherence to prescribed therapy presents managed care pharmacists with both a challenge and an opportunity. Improvements in the quality of care and clinical outcomes in patients with ACS or VTE can be achieved through managed care pharmacist efforts.

■ Conclusions

Some of the preventable morbidity, mortality, and costs associated with ACS and VTE can be avoided by improving the use of anticoagulant and antiplatelet therapy in patients with these conditions. Efforts by managed care pharmacists can contribute to these goals.

DISCLOSURES

Randall D. Seifert discloses that there was no financial relationship or financial interest relating to the topic of this activity. Seifert was responsible for the entire study concept and design of this article. He performed all of the data collection, data interpretation, writing, and revision of this article.

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Applying Quality Measures and Guidelines in the Management of Acute Coronary Syndrome and Venous Thromboembolism

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Posttest Worksheet: Applying Quality Measures and Guidelines in the Management of Acute Coronary Syndrome and Venous Thromboembolism

- Which of the following is thought to be the most common preventable cause of hospital death?
 - Fatal non-ST-segment myocardial infarction (NSTEMI)
 - Fatal ST-segment myocardial infarction (STEMI)
 - Fatal pulmonary embolism (PE)
 - Fatal unstable angina (UA)
- Which of the following organizations spearheaded the Surgical Care Improvement Project?
 - Agency for Healthcare Research and Quality
 - Centers for Medicare & Medicaid Services
 - National Quality Forum
 - The Joint Commission
- Which of the following is the recommended duration of dual antiplatelet therapy in American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for patients with UA/NSTEMI?
 - 7 days
 - 30 days
 - 6 months
 - 12 months
- Which of the following statements about reperfusion therapy for patients with STEMI is correct?
 - Percutaneous coronary intervention (PCI) is preferred if it can be performed within 90 minutes after presentation.
 - PCI is preferred if it can be performed within 24 hours after diagnosis.
 - Thrombolysis is preferred if it can be performed within 90 minutes after diagnosis.
 - Thrombolysis is preferred if it can be performed within 24 hours after diagnosis.
- Which of the following is taken into consideration in thrombolysis in myocardial infarction risk scoring for patients with NSTEMI or UA?
 - Aged ≥ 50 years
 - Elevated serum cardiac markers
 - New onset chest pain at the time of presentation
 - Use of warfarin in the preceding 7 days
- Which of the following is an advantage of unfractionated heparin (UFH) over enoxaparin in a patient with NSTEMI or UA who is undergoing cardiac catheterization?
 - Lower risk of heparin-induced thrombocytopenia
 - More consistent level of anticoagulation
 - Greater ease of administration
 - More ready reversal of anticoagulant effects if bleeding occurs
- According to ACC/AHA guidelines, which of the following agents is preferred for patients with NSTEMI or UA who are at increased risk for bleeding when a conservative treatment approach is chosen?
 - Bivalirudin
 - Fondaparinux
 - Enoxaparin
 - UFH
- Fondaparinux should be avoided in patients with NSTEMI who plan to undergo PCI because of the high risk of
 - bleeding.
 - catheter-related thrombi.
 - recurrent myocardial infarction (MI).
 - thrombocytopenia.
- Which of the following statements about the risks associated with the use of coronary stents is correct?
 - There is no difference between bare-metal and drug-eluting stents in the 1-year risk of stent thrombosis, death, or MI.
 - There is a small increase in stent thrombosis after 1 year in patients with drug-eluting stents compared with patients with bare-metal stents, but it is accompanied by a decreased risk for death or MI.
 - There is a small increase in stent thrombosis after 1 year in patients with bare-metal stents compared with patients with drug-eluting stents, but it is not associated with an increased risk for death or MI.
 - There is a small increase in stent thrombosis after 1 year in patients with drug-eluting stents compared with patients with bare-metal stents, but it is not associated with an increased risk for death or MI.

Posttest Worksheet: Applying Quality Measures and Guidelines in the Management of Acute Coronary Syndrome and Venous Thromboembolism

10. Which of the following statements about the risk for VTE in medical and surgical patients with brief hospital stays is correct?
 - a. If VTE does not occur during hospitalization, it is not likely to occur after discharge.
 - b. VTE may occur after hospitalization and usually occurs anytime within the first month after discharge.
 - c. VTE may occur after hospitalization and usually occurs anytime within the first 3 months after discharge.
 - d. VTE may occur after hospitalization and usually occurs anytime within the first year after discharge.
11. Which of the following interventions is preferred for VTE prophylaxis in general surgery patients?
 - a. Aspirin
 - b. Early and aggressive ambulation
 - c. Low-dose UFH or LMWH
 - d. Warfarin
12. Which of the following statements about strategies to promote the use of VTE prophylaxis when it is warranted is correct?
 - a. Combinations of strategies are more effective than a single strategy.
 - b. Electronic decision-support systems are more effective than paper-based reminders.
 - c. Prophylaxis default systems are more effective than risk assessment scoring systems.
 - d. Risk recognition systems are more effective than prophylaxis default systems.
13. Which of the following is a potential advantage of the use of LMWH over LDUH for an acutely ill medical patient at risk for VTE?
 - a. Lower drug acquisition cost
 - b. Lower risk for major bleeding
 - c. Lower risk for HIT
 - d. Lack of risk for injection site hematoma
14. Which of the following statements about the results of the EXCLAIM trial of extended-duration prophylaxis using enoxaparin in acutely ill medical patients at high risk for VTE is correct?
 - a. It had no effect on the risk for VTE.
 - b. It significantly reduced the risk for VTE.
 - c. It significantly reduced all-cause mortality.
 - d. It did not increase the risk for major bleeding.
15. Which of the following statements about warfarin therapy in patients with VTE is correct?
 - a. It should be avoided in patients receiving UFH, LMWH, or fondaparinux because of the risk of hemorrhage from excessive anticoagulation.
 - b. It should be initiated the day after discontinuing UFH, LMWH, or fondaparinux to provide continuous anticoagulation.
 - c. It should be initiated 5 days after discontinuing UFH, LMWH, or fondaparinux to minimize the risk of hemorrhage from excessive anticoagulation.
 - d. It should be overlapped with UFH, LMWH, or fondaparinux by at least 5 days because of the hypercoagulable state during initial warfarin therapy.
16. Which of the following is the preferred duration of warfarin therapy for a patient with a first episode of VTE due to a transient, reversible cause?
 - a. 30 days
 - b. 6 weeks
 - c. 3 months
 - d. 12 months
17. Cost savings from using LMWH instead of UFH to treat patients with VTE are primarily due to a
 - a. lower cost of initial care.
 - b. lower cost of long-term complications.
 - c. lower drug acquisition cost.
 - d. shortened hospital stay.
18. Which of the following might be used to promote program participation and adherence to prescribed therapy by managed care patients with ACS or VTE except?
 - a. Evidence-based guidelines
 - b. Pay-for-performance financial incentives
 - c. Pharmacist-based medication therapy management with reconciliation
 - d. Reduced premiums or copayments for medications
19. Patients with ACS and drug-eluting stents who fail to adhere to prescribed long-term clopidogrel therapy are at increased risk for
 - a. costly rehospitalization and death.
 - b. costly rehospitalization, but not death.
 - c. death, but not costly rehospitalization.
 - d. neither costly rehospitalization or death.
20. Which of the following characteristics in patients with ACS and drug-eluting stents increases the risk of nonadherence to prescribed long-term clopidogrel therapy?
 - a. College education
 - b. Married status
 - c. Pre-existing cardiovascular disease
 - d. Provision of discharge instructions

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