Disease-a-Month®

Volume 51 Number 2/3 February/March 2005

Venous Thromboembolism

Joseph A. Caprini, MD, MS, FACS, RVT, FACPh
Louis W. Biegler Chair of Surgery and Director of Surgical and Vascular Research, Evanston Northwestern Healthcare;
Professor of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL;
Professor of Biomedical Engineering, Robert R. McCormick School of Engineering & Applied Science, Northwestern University, Evanston, IL

Joann Lohr, MD, FACS, RVT
Director of The John J. Cranley Vascular Laboratory, Good Samaritan Hospital, Cincinnati, OH

Victor F. Tapson, MD
Associate Professor of Medicine, Division of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, NC

Michael H. Salinger, MD, FACC, FSCAI
Director, Interventional Cardiology, Evanston Northwestern Healthcare;
Associate Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

Ted E. Feldman, MD, FACC, FSCAI
Director, Cardiac Catheterization Laboratories, Evanston Northwestern Healthcare;
Professor of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL

John E. Rectenwald, MD
Vascular Surgery Fellow, Section of Vascular Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI

Thomas W. Wakefield, MD
S. Martin Lindenauer Professor and Head, Section of Vascular Surgery, Department of Surgery, University of Michigan, Ann Arbor, MI

Ann K. Wittkowsky, PharmD, CACP, FASHP
Clinical Professor, University of Washington School of Pharmacy;
Director, Anticoagulation Services, University of Washington Medical Center, Seattle, WA

Bruce L. Davidson, MD, MPH
Clinical Professor of Medicine, Pulmonary and Critical Care,
University of Washington School of Medicine, Swedish Medical Center, Seattle, WA

Witold Z. Tomkowski, MD
Professor of Medicine, Cardio-Pulmonary Intensive Care,
National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland

Anthony J. Comerota, MD, FACS
Clinical Professor of Surgery, University of Michigan
Director, Jobst Vascular Center, The Toledo Hospital, Toledo, OH

Hugo Partsch, MD
Professor of Dermatology and Angiology, Emeritus Head, Dermatological Department,
Wilhelminen Hospital, Medical University of Vienna, Vienna, Austria

Theodore E. Warkentin, MD, FRCP(C), FACP
Professor, Department of Pathology and Molecular Medicine and Department of Medicine,
McMaster University;
Associate Head, Transfusion Medicine, Hamilton Regional Laboratory Medicine Program;
Hematologist, Service of Clinical Hematology,
Hamilton Health Sciences, Hamilton, Ontario, Canada

Agnes Y. Y. Lee, MD, MSc, FRCP(C)
Associate Professor, Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Thomas M. Hyers, MD
Clinical Professor of Medicine, St. Louis University School of Medicine, St. Louis, MO

Alessandra Puggioni, MD
Fellow, Division of Vascular Surgery, Mayo Clinic and Foundation, Rochester, MN

Manju Kalra, MBBS
Assistant Professor of Surgery, Mayo Clinic College of Medicine,
Division of Vascular Surgery, Mayo Clinic and Foundation, Rochester, MN

Peter Gloviczki, MD
Professor of Surgery, Mayo Clinic College of Medicine, Chair, Division of Vascular Surgery;
Director, Gonda Vascular Center, Mayo Clinic and Foundation, Rochester, MN

Frank T. Padberg, Jr, MD
Professor of Surgery, Division of Vascular Surgery, Department of Surgery, New Jersey
Medical School, University of Medicine and Dentistry of New Jersey;
Chief, Section of Vascular Surgery, VA New Jersey Health Care System, Newark, NJ

Alex C. Spyropoulos, MD, FACP, FCCP
Medical Director, Clinical Thrombosis Center, Lovelace Sandia Health Systems;
Clinical Associate Professor of Medicine, Associate Professor of Pharmacy, University of New Mexico Health Sciences Center/College of Pharmacy, Albuquerque, NM

Walter Ageno, MD
Associate Professor of Medicine, University of Insubria, Varese, Italy

Alexander G. G. Turpie, MD, FRCP, FRCPC, FACC
Professor of Medicine, McMaster University, Hamilton, Ontario, Canada

Bo Eklöf, MD, PhD
Emeritus Clinical Professor of Surgery,
John A. Burns School of Medicine, University of Hawaii, Honolulu, HI;
University of Lund, Sweden

Dejan Maksimovic, BS
Medical student, College of Osteopathic Medicine, Des Moines University, Des Moines, IA

Catherine Glase, BS
Student in the Accelerated Masters of Nursing program, DePaul University, Chicago, IL

Jack Ansell, MD
Professor of Medicine, Boston University School of Medicine;
Vice Chair for Clinical Affairs, Department of Medicine,
Boston University Medical Center, Boston, MA

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Foreword

It looks like spring in Washington, DC. The days are getting warmer, people are out and about. The rituals of renewal with flower planting, yard work and spring cleaning are about to begin. Of course I had previously heard and read about the cherry blossoms around the tidal basin at the Jefferson Memorial but this was the first year I was able to experience them on a morning run with the sun just rising. I was awestruck by nature. If you have never seen our nation's capital in the spring, you should make a mental note to add it to the "100 places to visit before I die" list.

Just as we look to renewal at home and work, it is once again time to look at the renewal of the Editorial Board here at Disease-a-Month. Many of the individuals on the Board have and will continue to serve to bring interesting and important monographs each month. We would like to hear from our readers if they have in mind a particular person who may contribute. Nominate your mentor, your friend or yourself. Please send in the names with a brief bio, which will help us in our deliberations.

This month Dr. Joseph Caprini has brought together a "tour de force" of experts from around the country. We have decided to publish this monograph "Venous Thromboembolism" as a double issue as the text is interrelated with one chapter building on the next. Read, learn and enjoy!

Janis M. Orlowski, M.D.
Editor in Chief

Introduction

Joseph A. Caprini, MD

This monograph is designed to provide the clinical practitioner with a practical user's guide on the prevention, diagnosis, and treatment of venous thromboembolism (VTE). Despite much research and many recent advances, VTE remains a serious problem, which is often underestimated or ignored.

The monograph begins with a careful look at a schema of thrombosis risk assessment to evaluate the likelihood of a given individual developing a thrombotic complication. Next, there is a thoughtful look at bilateral duplex scanning for deep venous thrombosis (DVT). This technique can avoid missing important DVTs, particularly when used in a postoperative patient. Testing for the presence of VTE is then discussed, with particular reference to newer hematologic and radiologic modalities. Another critical topic is thrombophilia testing, when and where it should be employed. Strokes related to a venous thrombosis embolizing through the heart to the brain are discussed, to make the reader aware of this important problem.

Over the past several years the treatment of VTE has been broadened by the introduction of newer agents which provide some advantages over traditional anticoagulants. Certain management issues that have been shown on national surveys to be a problem are discussed. One of the most important issues is overlapping heparin and warfarin in the initial treatment of VTE. The facts underlying these principles are clearly presented and should provide the reader with some excellent practical guidelines.

Newer developments in the management of pulmonary embolism are presented to provide the reader with additional options. Among these are the fibrinolytic drugs. Indications and techniques involved in their use are discussed so that the physician doing the initial evaluation of VTE can help select appropriate candidates for this type of therapy.

One of the most poorly understood concepts in the treatment of DVT involves the use of compression bandages and stockings. Essential principles of this approach to manage acute DVT are presented. The

Dis Mon 2005;51:68-69
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.02.002

importance of heparin-induced thrombocytopenia as a problem is emphasized, particularly as it relates to the overall safety and cost of patient care. On some occasions, the least expensive heparin product can result in the most expensive complications.

An exciting area of exploration is the association between thrombosis and cancer, including the fascinating effect of low molecular weight heparin in prolonging patient survival in certain situations. One of the common dilemmas in the treatment of VTE is the length of prophylaxis with anticoagulants; the chapter on long-term use of various agents presents newer options and considerations for the clinician. Another poorly understood area is the concept of the postthrombotic syndrome. The long delay between the initial VTE event and the appearance of symptoms is discussed, along with newer management approaches.

The latest CEAP classification created by the American Venous Forum subcommittee is outlined in detail. Patients who require surgery or an invasive procedure who are on chronic anticoagulation require "bridging"; the availability of various low molecular weight heparins has created an improved schema for them. The latest guidelines for "bridging," along with the available data from recent trials, are presented for the reader.

One of the biggest current problems in the United States is lack of appropriate prophylaxis for medically ill hospitalized patients. A chapter on newer options and standard anticoagulants discusses this issue. Recently there has been a great deal of interest in problems associated with the occurrence of VTE in air travelers. These issues are presented, along with the latest results from clinical trials. Finally, advances in technology and chemistry have resulted in the emergence of newer oral anticoagulants. These products may change the anticoagulation landscape in a significant way over time.

Thrombosis Risk Assessment as a Guide to Quality Patient Care

Joseph A. Caprini, MD

Background

Venous thromboembolism (VTE) is a serious complication that is frequently encountered in medical and surgical practice. Approximately 2 million people each year will suffer from a deep vein thrombosis (DVT), and approximately 600,000 of these individuals will suffer a pulmonary embolism (PE), which is fatal in about 200,000 patients annually.[1] Pulmonary hypertension can be expected to develop in approximately 30,000 patients who survive their PE. The postthrombotic syndrome (PTS) will be seen in approximately 800,000 patients annually in the United States; 7% of these individuals will have a severe form of the problem and become permanently disabled.[2] One of the most troubling statistics is the fact that 50% of the 2 million cases of DVT yearly are "silent." Occasionally, the first sign or symptom of the disease is a fatal PE.[3] Furthermore, it has been estimated that approximately 1 of 20 hospitalized medical patients will suffer a fatal PE if they have not received appropriate thrombosis prophylaxis.[4]

Another serious complication of DVT is nonhemorrhagic stroke that may occur in a patient with a patent foramen ovale.[5] A clot in the deep venous system of the leg can break off and travel to the right atrium, dilating that heart chamber. If the patient is one of the 25 or 30% who have a nonfunctioning patent foramen ovale, this atrial dilatation can open the patent foramen and allow the clot to enter the left side of the heart and proceed to the brain, producing a stroke.[6] The diagnosis of this problem is difficult because once the right atrium returns to normal size, the patent foramen ovale may be difficult to detect. Often when the clot breaks off from the leg, it does so cleanly without residual damage that can be detected on subsequent duplex examination.[6]

Table 1 shows some of the commonly seen problems that at first glance

Dis Mon 2005;51:70-78
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.02.003

TABLE 1. Common manifestations of venous thromboembolism including required investigations to uncover all instances of the disease

Leg pain
Leg tenderness
Leg swelling
Chest pain
Shortness of breath
Transient or orthostatic hypotension
Transient hypoxemia
Unexplained decrease in level of consciousness
Suspected narcotic excess
Suspected postoperative myocardial infarction
Postoperative nonhemorrhagic stroke
Postoperative pneumonia
Unexplained sudden death
Unexplained cardiovascular collapse
Postoperative death without autopsy
90-day follow-up for death, readmission, outpatient treatment of VTE
5-year follow-up looking for signs of the postthrombotic syndrome

may not seem to be associated with a DVT. We recommend keeping a high level of suspicion for patients who exhibit these clinical manifestations. Not all of these problems will result in a fatal or serious outcome. They may predispose the patient to later develop the postthrombotic syndrome or have a higher incidence of DVT if they have a subsequent operative procedure.

The problem of long-term follow-up of patients is not easy to solve and many DVT events occur several weeks or longer after discharge. Readmissions, deaths, and outpatient treatment of DVT using low molecular weight heparin (LMWH) may be very difficult data for the surgeon to obtain. The average busy clinician may not associate a stroke or a variety of other postoperative symptoms as being caused by a postoperative DVT. It is no wonder that many feel that VTE is not a problem in their clinical practice.

Risk Assessment

The process of providing appropriate thrombosis prophylaxis to medical and surgical patients is a complex issue because many times the administration of powerful anticoagulants may carry the risk of side effects, most notably bleeding. The seventh American College of Chest Physicians' Consensus on antithrombotic and thrombolytic therapy has recently published a thorough evaluation of the literature that has been translated into evidence-based guidelines for thrombosis prophylaxis and

TABLE 2. Prophylaxis regimen

Total Risk Factor Score	Incidence of DVT	Risk Level	Prophylaxis Regimen
0–1	<10%	Low	No specific measures; early ambulation
2	10–20%	Moderate	ES or IPC or LDUH, or LWMH
3–4	20–40%	High	IPC or LDUH, or LMWH alone *or* in combination with ES or IPC
5 or more	40–80% 1–5% mortality	Highest	Pharmacological: LDUH, LMWH,* Warfarin,* or Fac Xa* alone *or* in combination with ES or IPC

Based on Geerts WH, Pineo GF, Heit JA, et al: Prevention of venous thromboembolism. Chest 2001; 119:132S–75S; Nicolaides AN, Breddin HK, Fareed J, et al: 2001 International consensus statement: prevention of venous thromboembolism guidelines according to scientific evidence; Caprini JA, Arcelus JI, et al: State-of-the-art venous thromboembolism prophylaxis. Scope 2001;8:228–240; Oger E: incidence of venous thromboembolism: a community-based study in western France. Thromb Haemost 2000; 657–660. Turpie AG, Bauer KA, Eriksson BI, et al: Fondaparinux vs. enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162(16):1833–40. ES, elastic stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; Fac Xa, Factor X Inhibitor.

treatment.[1] It is an excellent compilation of relevant medical literature as interpreted by some of the foremost authorities in the field. This document endorses the concept of thrombosis risk assessment, although they point out that individual formal risk assessment models have not been adequately validated, are cumbersome, and are infrequently used by the physician. They recommend a simplification of the process by assigning patients to one of four VTE risk levels based on type of operation, age, and the presence of additional risk factors (Table 2). Some of us feel that this approach leaves certain gaps in the implementation of prophylaxis and calculation of degree of risk. In certain cases the number of risk factors is so great that the patient's decision to have a quality-of-life procedure may be affected.[7] We feel that all possible risk factors need to be queried to identify the extent of risk for each individual patient. Thrombosis prophylaxis then needs to be individualized on the basis of the results of this analysis. If one misses any of these factors, the patient's thrombosis risk may not be properly estimated. In those with a double-digit point score, the risk may be extremely high and, although this has not been subjected to rigorous clinical trial to determine the degree of increased risk, still needs to be considered. Some patients may want to forgo elective quality-of-life procedures when the point score indicates an extremely high chance of VTE.

Thrombosis Risk Factor Assessment

Joseph A. Caprini, MD, MS, FACS, RVT
Louis W. Biegler Professor of Surgery,
Northwestern University
The Feinberg School of Medicine;
Professor of Biomedical Engineering,
Northwestern University;
Director of Surgical Research,
Evanston Northwestern Healthcare
Email: j-caprini@northwestern.edu
Website: venousdisease.com

Patient's Name:_____ Age: ___ Sex: ___ Wgt:___lbs

Choose All That Apply

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (< 1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > 25)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Other risk factors_____

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (> 45 minutes)
- ❑ Laparoscopic surgery (> 45 minutes)
- ❑ Patient confined to bed (> 72 hours)
- ❑ Immobilizing plaster cast (< 1 month)
- ❑ Central venous access

Each Risk Factor Represents 5 Points

- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ History of DVT/PE
- ❑ **Family history of thrombosis***
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other congenital or acquired thrombophilia

If yes:
Type_____
***most frequently missed risk factor**

For Women Only (Each Represents 1 Point)

- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

Interpretation of Risk Assessment Guidelines

Our group has been performing detailed individual risk assessment on medical and surgical patients since the late 1980s.[8] The latest version of this model is seen in Table 3. We use a hybrid approach which begins with evidence-based guidelines and consensus statements, combined with logic, emotion, and the experience of the interviewer. This approach was selected because it is the approach used by physicians when dealing with patients and their illnesses. If there is no available level 1 data or if the patient's circumstances would have resulted in them being excluded from

Prophylaxis Regimen

Total Risk Factor Score	Incidence of DVT	Risk Level	Prophylaxis Regimen	Legend
0-1	<10%	Low Risk	No specific measures; early ambulation	**ES** - Elastic Stockings **IPC** - Intermittent Pneumatic Compression **LDUH** - Low Dose Unfractionated Heparin **LMWH** - Low Molecular Weight Heparin **Fac Xa** - Factor X Inhibitor
2	10-20%	Moderate Risk	ES or IPC or LDUH, or LWMH	
3-4	20-40%	High Risk	IPC or LDUH, or LMWH alone *or* in combination with ES or IPC	
5 or more	40-80% 1-5% mortality	Highest Risk	Pharmacological: LDUH, LMWH*, Warfarin*, or Fac Xa* alone *or* in combination with ES or IPC	

Prophylaxis Safety Considerations: Check box if answer is 'YES'

Anticoagulants: Factors Associated with Increased Bleeding
❑ Is patient experiencing any active bleeding?
❑ Does patient have (or has had history of) heparin-induced thrombocytopenia?
❑ Is patient's platelet count <100,000/mm^3?
❑ Is patient taking oral anticoagulants, platelet inhibitors (e.g. NSAIDS, Clopidigrel, Salicylates)?
❑ Is patient's creatinine clearance abnormal? If yes, please indicate value _____
If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and should consider alternative prophylactic measures.
Intermittent Pneumatic Compression (IPC)
❑ Does patient have severe peripheral arterial disease?
❑ Does patient have congestive heart failure?
❑ Does patient have an acute superficial/deep vein thrombosis?
If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and should consider alternative prophylactic measures.

Based on: Geerts WH et al: Prevention of Venous Thromboembolism. Chest 2001; 119:132S-175S; Nicolaides AN et al: 2001 International Consensus Statement: Prevention of Venous Thromboembolism, Guidelines According to Scientific Evidence; Caprini JA, Arcelus JI et al: State-of-the-Art Venous Thromboembolism Prophylaxis. Scope 2001; 8: 228-240; and Oger E: Incidence of Venous Thromboembolism: A Community-based Study in Western France. Thromb Haemost 2000; 657-660. Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs. Enoxaparin for the Prevention of Venous Thromboembolism in Major Orthopedic Surgery: A Meta-analysis of 4 Randomized Double-Blind Studies. Arch Intern Med 2002; 162(16):1833-40. Ringley et al: Evalution of pulmonary..intermittent pneumatic compression boots in congestive heart failure. American Surgeon 2002; 68(3): 286-9. Morris et al. Effects of supine intermittent compression on arterial inflow to the lower limb. Archives of Surgery 2002. 137(11):1269-73.

Examining Physician's Signature: _____ Date: _____

a randomized trial, they still need to be treated in the best manner possible using a combination of science, logic, emotion, and experience.[9]

Case Study

One practical example of this principle would be a 62-year-old morbidly obese male requiring arthroscopic knee surgery on the left leg. The patient has a past history of venous thrombosis after cholecystectomy 20 years ago, and 4 years ago had successful surgical treatment for

prostate cancer. The point score for this patient using our model is 9 and includes 2 each for surgery, cancer, and age over 60 years, and 3 for past history of DVT.[10] There is no specific trial that would address this clinical situation. If one looks at the Chest Guidelines, thrombosis prophylaxis for outpatient arthroscopic surgery is not recommended unless additional risk factors are present. There are no specific guidelines regarding the intensity or duration of prophylaxis. The Consensus Guidelines are based on clinical trial data and many clinical trials would exclude patients with a past history of venous thrombosis, such as the individual in this example. The question is what this patient's risk is and what prophylaxis, if any, should be used. According to our risk scoring system, the patient's point total is 9 and we know, according to Chest Consensus Guidelines, that patients with more than five risk factors are in the very high-risk group and have a 40 to 80% chance of developing a venous thrombosis with up to 5% mortality.[1]

Length of Prophylaxis

Furthermore, we know that abdominal surgery cancer patients, who are also in this very high-risk group, when given 30 days of LMWH, have a statistically significantly lower incidence of thrombosis than when 7 days of prophylaxis are used.[11] If one were to apply the Caprini score to the average patient in this trial, the following calculations would be done. We would assign 2 points each for abdominal surgery, cancer, and age over 60 years for a total score of 6. Since our hypothetical arthroscopic surgical patient has a score of 9, we could extrapolate that he should receive at least 30 days of LMWH prophylaxis postoperatively. This regime significantly reduced the incidence of DVT in abdominal surgery patients who had an estimated score of 6 as noted above. The all cause fatality rate in this trial for those receiving 30 days of the drug was 0.3%. Quite an improvement compared to the up to 5% fatal PE death rate in those in the highest risk group not receiving prophylaxis as quoted in the Consensus Guidelines.

Personal or Family History of VTE

One of the most frequently missed risk factors is a past history or family history of VTE. In our practice 56% of patients with a past history of thrombosis were found to have a positive marker for thrombophilia, while 42% of patients with a family history of thrombosis were found to have a positive marker.[12] We feel that a history or family history of VTE in combination with patients having

a major operation is sufficient to classify an individual in the very high-risk group.[13]

Obstetrical History

Another important and frequently overlooked risk factor occurs in women with a past history of an obstetrical complication including a stillborn, miscarriage in any trimester, premature birth with toxemia, or growth-restricted infant. These past events may be the clinical manifestation of a serious thrombophilia defect known as anticardiolipin antibodies, which includes the lupus anticoagulant.[14-19] We also are careful to question patients about a history or family history of stroke, since, in some of these individuals, elevated levels of homocysteine have been found and this is easily treated with vitamin prophylaxis.[20-22]

Long-Term Prophylaxis

The length of prophylaxis in postoperative patients is important. Except for certain orthopedic and general surgical populations, not many studies have been done to show the benefit of long-term prophylaxis. In the above-mentioned groups we know that statistically significant lowering of the venographic incidence of venous thrombosis has been achieved with 4 to 6 weeks of postoperative prophylaxis using various pharmacologic agents.[23,24] One thing to keep in mind when deciding about long-term prophylaxis is the mobility of the patient. Seriously ill patients are discharged with fistulas, draining wounds, or intravenous catheters for nutritional support or antibiotic treatment. These individuals spend most of the time in a recliner, which is not early ambulation but rather early angulation.

Efficacy versus Safety

One of the most important considerations regarding the choice of thrombosis prophylaxis is to balance efficacy and safety concerns. Many times clinicians use inadequate prophylaxis because of a concern for bleeding despite the fact that some of these patients are already at enormously high risk. It is natural for a surgeon to consider bleeding to be a surgical problem and thrombosis to be an act of God. We would like to suggest a different philosophy. Depending upon the patient's level of risk, one may require a type or intensity of prophylaxis that may increase their chances of bleeding. These increased risks, however, can be justified by the very high incidence of fatal PE or disabling stroke. We feel it is important to have a preoperative discussion with patients and their families regarding the relative risks and benefits of a particular thrombo-

sis prophylaxis strategy. This should include a realistic evaluation of the risk of serious venous thromboembolic complications. One must also remember that if the patient is at very high risk and thrombosis prophylaxis has to be discontinued in the early postoperative period due to bleeding, the chances of a serious event are magnified. Patients undergoing quality-of-life procedures must weigh the risks and benefits of such procedures if they are in this very high-risk group.

Finally, we feel that a careful individual assessment of thrombosis risk must be done in every patient to minimize the morbidity and mortality of venous thromboembolic events. As a part of this analysis, the length of prophylaxis needs to be determined based on the patient's individual circumstances.

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Bilateral Lower Extremity Duplex Scanning Revisited

Joann Lohr, MD, FACS, RVT

Introduction

Noninvasive vascular laboratories have adopted varying policies regarding examinations for deep venous thrombosis (DVT). Some laboratories examine limbs unilaterally, whereas others have a bilateral policy.[1] Duplex imaging is painless and noninvasive and does not require injecting contrast material. It has rapidly replaced venography as the first line of investigation for diagnosing DVT. Acute DVT is responsible for more than 600,000 hospitalizations each year and has a 1-year mortality rate of 21%.[2-5] Because of its accuracy and noninvasive characteristics, duplex ultrasound scanning has become the diagnostic test of the choice for detection of DVT. Examinations routinely have been performed on both legs because of easy patient acceptance and the finding that there is a high incidence rate of unsuspected thrombi in the contralateral limb.[4,6,7] The clinical significance of contralateral thrombi has been debated. In time studies it takes only 5 to 6 minutes to completely scan a second limb: the patient needs to complete the history questionnaire and risk factor assessment, change clothes, turn over, and redress, which are all components of a unilateral or bilateral scan. Timesaving in a busy vascular laboratory is very limited. The ability to cluster these patients, even in laboratories that use a selective scanning protocol for the second limb, is unpredictable. It is very difficult to capture these small time savings and put them to practical use.

This study was undertaken to analyze the need for bilateral duplex imaging and, if possible, to identify the population in which unilateral study was appropriate.

Patients and Methods

This retrospective study examined all bilateral duplex venous scans performed in a 2-year time period. The laboratory is staffed by three full-time and one part-time vascular technologists, which average 14.25

Dis Mon 2005;51:79-85
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.001

years of clinical experience. The vascular resident is in full-time attendance to assist with any problems or questions. A total of 3425 consecutive bilateral venous duplex scans were entered into a computerized database. All results along with symptoms and risk factors at the time of the scan were entered by one individual into a computerized database. Any follow-up scans on the same patients who were sequentially scanned within the initial 6-month time period of the original study were not included in this review.

Symptoms were recorded and defined as pain, swelling, discoloration, and tenderness. Risk factors collected and analyzed included the following: previous history of DVT and superficial vein thrombosis (SVT), history of trauma, oral contraceptives, cancer, hypercoagulopathy, varicose veins, vein stripping, pulmonary embolus, heart disease, diabetes, drug abuse, surgery, smoking status, and pregnancy.

Data were analyzed using the BMDP statistical software (University of California Press, Berkeley, CA). Parametric statistical analyses were made using Student's *t*-test, whereas nonparametric comparisons were made using the χ^2 method. For all possible subsets, regression analysis (BMDP 9R) was used to estimate a regression equation for "best" subsets of predictor variables.

All duplex scans were performed with a 10-MHz phased annular array probe on a commercially available venous duplex machine (Phillips ATL, Ultramark 9000 ATL). Scans were performed on both limbs in accordance with a standard laboratory protocol that required all scans to be bilateral. When a unilateral scan was ordered for charge purposes and billing, only unilateral charges were entered. Thrombi were characterized and aged, and a technologist's data sheet was completed at the end of each procedure. The data sheet indicated the veins visualized and classified the zones involved in thrombosis. These zones were used to report and localize identified thrombi and to localize the segments of veins that were not imaged.

The studies were performed with the patients positioned at 15^{o} to 30^{o} in the reversed Trendelenberg position. The limb was slightly abducted and externally rotated. The posterior calf was examined whenever possible with the patient lying face down. The femoral vessels were generally approached first. The venous bifurcation was best visualized distal to the arterial bifurcation, and the deep femoral vein was best seen in that portion. Only a very short segment of the deep femoral vein, near its origin, was visualized as it rapidly angles deep and is normally visualized for approximately 5 cm, corresponding to Zone 2.3. The superficial vein was visualized, usually in continuity, down to the proximal abductor

canal at Zone 4.2. When scanning was done with portable equipment, calf vein visualization was limited because of positioning difficulties and artifact.

Acute thrombi judged to be totally occlusive may demonstrate a free-floating thrombus tip, clot retraction, or vein wall distension. Acute clots are soft, with smooth characteristics demonstrating faint echogenicity and homogeneity; there are no collaterals and no evidence of recanalization. In contrast, chronic clots may be partially compressible and are usually adherent to the vein wall. Collaterals may be identified and may be contracted, firm, and irregular with brightly echogenic material that may be heterogenous. Indeterminate thrombi share characteristics of both acute and chronic thrombi to the point where exact aging may be difficult.

Dr. John J. Cranley always taught the vascular residents that "seeing is believing"[8]: If a clot is visualized, it is there: and if a normal vein is visualized, it is indeed normal. Venograms were obtained only if a scan was of poor quality, a suspicion that the B-mode was incorrect, or if a venogram was needed to place an inferior vena cava filter.

Results

Of the 3425 studied, 37% were male and 63% were female. Inpatients were 33% and outpatients were 67%. Eighty-two percent of the scans were negative and 18% (608) of the scans were positive for thrombosis. Five hundred sixteen of the scans were positive for unilateral DVT and 92 were positive for bilateral DVT. The left limb was involved in 280 thrombi, while 236 thrombi were found in the right limb. Of the patients with the thrombus identified, 92% were acute, 2.5% were indeterminate, and 5.5% were chronic. Ninety-two patients had bilateral DVTs identified. Of these, 46 had unilateral symptoms and 12 had no symptoms in either limb but bilateral thrombosis was identified. Five-hundred sixteen patients had unilateral DVT. Of these patients, 385 had thrombus identified in their symptomatic leg; however, 30 patients had symptoms in the contralateral limb and 62 patients were completely asymptomatic and had a unilateral DVT identified. An additional 12 patients were asymptomatic and had a bilateral DVT identified. Forty-six patients who had bilateral DVT identified had symptoms in one leg but not in the second leg. If we analyze the thrombi in limbs that were asymptomatic, we see that calf vein thrombi were most frequently identified but proximal thrombi were identified in limbs that were asymptomatic (Table 1). Multiple vein segments were frequently involved.

TABLE 1. Asymptomatic limb thrombi

Clot Location	Bilateral Clots, Asymptomatic Bilaterally (n = 12)	Unilateral Clots, Asymptomatic Bilaterally (n = 62)	Bilateral Clots, Unilateral Symptoms (n = 46)	Unilateral Clots, Contralateral Symptoms (n = 30)	Total Clots for Each Location
CFV	2	5	18	3	28
SFV	3	12	28	5	48
DFV	3	5	17	2	27
GSV	3	11	28	2	44
DTV	12	31	46	5	94
ATV	1	0	14	0	15
POP	2	15	29	4	50
PER	21	31	48	7	107
SOL	20	23	53	22	118
LSV	2	9	43	12	66
PERF	0	1	1	0	2
ACV	0	0	2	2	4
BKV	0	0	8	1	9
Total number of clots = 612					

*Several patients had more than one vein segment involved in thrombosis.

Discussion

Venous thromboembolism can present in a variety of clinical situations. Trauma, malignancy, intravenous catheters, prosthetic vascular surfaces, travel, dehydration, endothelial injury, hyperviscosity, external compression, and venous stasis may all precipitate venous thrombosis. Immobilization, surgery, anesthesia with muscle relaxants, pregnancy, and local pressure may all be associated with stasis. Virchow's triad is as true now as it had been when first identified. Other factors that have also been linked with an increased risk of thrombosis include age greater than 40, use of oral contraceptives, and obesity. Systemic diseases that may predispose thromboembolism formation include systemic lupus erythematosus, essential thrombocythemia, lupus anticoagulant, nephrotic syndrome, Behcet's disease, paroxysmal and nocturnal hemoglobinuria, polycythemia vera, and hyperviscosity syndromes. Clinically, the diagnosis of DVT is very difficult. The physical indications of venous thromboembolism depend on two processes. The first process is swelling and increased temperature in the lower extremity due to obstruction of the venous outflow. In as many as 80% of cases, ankle edema in one limb is a sign of underlying thrombosis. The second process is the inflammatory response of phlebitis, which produces localized pain and tenderness with or without swelling and increased temperature. Localized tenderness is reportedly present in as many as 50% of cases; however, pain on

dorsiflexion of the toe (Homans' sign) is unreliable and present in only 8% of cases. Although these are the classic findings of DVT, many or all may be lacking even when thrombosis is extensive. The extent of phlebitic process is not related to the degree of inflammatory changes, and why phlebitis occurs in only some cases and not all is unknown. Browse has said, "It would be much more realistic to ignore physical signs and work on the assumption that one-third of all patients in the hospital have thrombi in their deep veins.[9]

Greenfield reported that only 40% of patients with venous thrombosis had any clinical signs of the disorder and that false-positive clinical signs occurred in as many as 50% of patients studied.[10] According to these data, 12% (74 patients) of 608 patients with DVT were completely asymptomatic. An additional 76 patients with DVT were free of symptoms in the involved limb or had symptoms that did not match the duplex scan findings.

Because of the inaccuracy of clinical examination, duplex scanning has rapidly become the workhorse of the vascular laboratory and has been accepted as the gold standard for diagnosing DVT. Routine venography is no longer obtained for comparison with duplex results in our hospital. This can become problematic with quality assurance. Reproducibility studies have replaced venography as a way to confirm and validate data. Duplex scans are noninvasive and repeatable; they may be performed quickly, and the equipment is portable. The most commonly reported sources of error using venous compression ultrasound include infrapopliteal thrombosis, segmental incompressibility, nonobstruction focal DVT, and venous duplication. Nix and coworkers reported that a thrombus would have been missed in only 0.9% of patients if unilateral scans alone were performed.[11] Based on their results, they perform unilateral scanning when a patient has unilateral symptoms of pain and tenderness without a history of joint replacement, malignancy, trauma, or symptoms of pulmonary embolism. Kerr and associates found 131 bilateral thrombi in 1084 duplex scans; however, not all patients had both extremities scanned.[12] The incidence of DVT among patients undergoing total joint replacement is reportedly as high as 35% in the nonoperated limb.

If venous thromboembolism is considered to be a systemic disease that manifests itself locally, then doing unilateral limited compression ultrasonography (common femoral and popliteal veins only) on a patient at risk for DVT seems inadequate. How many vascular laboratories scan only one carotid artery when asked to screen a patient at high risk for stroke? The value in examining both sides when screening for DVT is the

added information that might alter management in relation to the duration of treatment or further investigations for hypercoagulable states. This becomes important when the contralateral asymptomatic limb is scanned and evidence of DVT is detected.

Unfortunately, clustering patients who have the potential for unilateral scanning and time salvage is problematic in a busy vascular laboratory. This timesaving does not equate to improved scheduling of patients and frequently is not available in utilizable segments. Blebea and coworkers concur that the time saving accrued with unilateral scanning may not amount to any cost saving.[13] The unilateral leg CPT code (93971) is reimbursed by Medicare only one dollar less than a bilateral study, so the cost saving is not significant. The clinical significance of the thrombi found in an asymptomatic limb is a source of ongoing debate.

In this study, we did not determine a subgroup that could safely and reliably undergo a unilateral scan. The clinical determination of DVT is also unreliable. We believe bilateral lower extremity duplex scans should be routinely performed on patients with suspected DVT. In addition to detecting asymptomatic DVT, this strategy allows for comparing limbs based on an anatomic variable, and it also avoids aberrant false-negative studies. Evaluating the second limb adds less than 6 minutes to the scanning time. DVT is extremely good at masquerading, as shown by 26% of the population whose symptoms did not match the anatomic and physiologic findings of duplex scanning. We believe these results support a policy of routine bilateral venous duplex scanning. This also obviates the potential that the patient can come back at a later date with a thrombus in the opposite leg. We will be unable to know if this thrombus is a new thrombosis, acute, chronic, or mixture, or a result of failure of prior treatment. In today's litigious society, given the ease of duplex scanning, it is unclear what the exact cutoff for missing a thrombus on the contralateral side should be. Recent events in the Mid East involving the NBC reporter David Bloom, as well as the recent public alert data, are increasing our public awareness of this preventable cause of death.[14] Patients need health care professionals to be their advocates; just because you can study one limb does not make this an appropriate choice for the evaluation of a systemic disease process.

Acknowledgments

The author acknowledges Hatton Research Staff members: Phuong Huynh, James Duffy, and Wendy Thompson, MS, who helped collect and analyze the data.

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The Diagnosis of Acute Venous Thromboembolism

Victor F. Tapson, MD

Clinical Manifestations: Symptoms and Signs

Venous thromboembolism (VTE) encompasses the spectrum of deep venous thrombosis (DVT) and pulmonary embolism (PE). The diagnostic approach generally depends on which of these first results in symptoms. Autopsy studies have repeatedly documented the high frequency with which PE has gone unsuspected and thus undetected.[1,2]

While the symptomatic presentation of DVT depends to some degree on the extent of thrombosis, it is clear that very large thrombi may evolve and never result in DVT symptoms but present first as symptomatic or even fatal PE. Unfortunately, the history and physical examination for acute DVT and PE are notoriously insensitive and nonspecific.[3-5] Patients with DVT often do not exhibit warmth, erythema, pain, swelling, or tenderness. Pain with dorsiflexion of the foot (Homans' sign) may be present in the setting of DVT but this finding is neither sensitive nor specific. The common symptoms and signs, including dyspnea, chest pain, tachypnea, and tachycardia, as well as less common findings, are nonspecific. Syncope and/or sudden death may occur with massive PE.

The differential diagnosis for acute DVT and for PE depend on the clinical presentation and the presence of concomitant disease. Cellulitis, musculoskeletal pain, trauma, a ruptured Baker's cyst, or asymmetric edema unrelated to DVT may result in symptoms and signs compatible with acute DVT. Pulmonary embolism can be confused with a flare of asthma or chronic obstructive lung disease, pneumothorax, acute bronchitis or pneumonia, anxiety with hyperventilation, heart failure, angina or myocardial infarction, musculoskeletal pain, rib fracture, pericarditis, pleuritis from collagen vascular disease, intrathoracic cancer, and occasionally, intraabdominal processes such as acute cholecystitis. Acute PE can be superimposed upon another underlying cardiopulmonary disease, upon which new or worsening symptoms are sometimes blamed.

Dis Mon 2005;51:86-93
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.002

Blood Tests

Acute PE is commonly associated with hypoxemia. Some individuals, particularly young patients without underlying lung disease, may have a normal PaO_2 even rarely a normal alveolar-arterial difference.[4,5] A sudden decrease in the PaO_2 or in the oxygen saturation in a patient unable to communicate an accurate history (eg, a demented or mechanically ventilated patient) suggests the possibility of acute PE.

The use of plasma measurements of circulating D-dimer (a specific derivative of cross-linked fibrin) in patients with acute PE has been extensively evaluated.[6] A normal enzyme-linked immunosorbent assay (ELISA) appears sensitive in excluding PE, particularly when the clinical suspicion is relatively low. A number of D-dimer assays are available, and the sensitivity and specificity of these assays vary. A positive D-dimer test means that DVT or PE is possible, but the lack of specificity dramatically limits this result. This tenet makes the use of D-dimer very limited in hospitalized patients in whom infection, cancer, trauma, and other disease states are common, and frequently associated with a positive assay.

Clinical probability scores based upon simple clinical parameters have been used together with a negative D-dimer to help exclude PE. In one prospective clinical trial, the SimpliRed D-dimer test (a rapid red blood cell agglutination D-dimer assay) was used together with simple scoring parameters readily available in the emergency department.[7] Of the 437 patients with a negative D-dimer result and low clinical probability in this study, only one developed PE during follow-up (Table 1). Whether or not such scoring systems are used in actual clinical practice, D-dimer assays may prove increasingly useful in excluding acute DVT and PE, particularly when low clinical suspicion supports its absence.

Both cardiac troponin T and troponin I levels have been found to be elevated in acute PE.[8,9] Troponin is specific for cardiac myocyte damage, and the right ventricle appears to be the source of this enzyme elevation in acute PE, and in particular, in more massive embolism in which myocyte injury due to right ventricular strain might be expected. Troponin levels cannot, however, be used like D-dimer testing; that is, they are not sensitive enough to rule out PE when clinical suspicion is relatively low, without additional diagnostic testing.

Electrocardiography and Chest Radiography

Electrocardiographic abnormalities are present in the majority of patients with acute PE. While ST-segment abnormalities, T-wave

TABLE 1. Determining pretest probability of acute PE using point system and D-dimer result[16]

Variable	Points
DVT symptoms/signs	3.0
PE as or more likely*	3.0
HR >100 beats/min	1.5
Immobilization/surgery†	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Total Score	**Pretest Probability‡**
<2.0	Low
2.0 to 6.0	Moderate
>6.0	High

DVT, deep venous thrombosis; PE, pulmonary embolism; HR, heart rate.

*PE as likely or more likely than an alternative diagnosis. Physicians were told to use clinical information, along with chest radiography, electrocardiography, and laboratory tests.

†If in previous 4 weeks.

‡Of the 437 patients with a negative D-dimer result and low clinical probability, only one developed PE during follow-up; thus, the negative predictive value for the combined strategy of using the clinical model with D-dimer testing in these patients was 99.5%.

changes, and left- or right-axis deviation are common, they are nonspecific. Only one-third of patients with massive or submassive emboli have manifestations of acute cor pulmonale such as the S1 Q3 T3 pattern, right bundle branch block, P-wave pulmonale, or right-axis deviation. The utility of electrocardiography in suspected acute PE is best characterized by its ability to establish or exclude alternative diagnoses, such as acute myocardial infarction.[4]

The chest radiograph is also often abnormal in patients with acute PE, but is also nearly always nonspecific. Common radiographic findings include atelectasis, pleural effusion, pulmonary infiltrates, and mild elevation of a hemidiaphragm.[4] Classic findings such as Hampton's hump or central pulmonary prominence with decreased peripheral vascularity (Westermark's sign) are suggestive of the diagnosis, but are infrequent.

Deep Venous Thrombosis: The Radiographic Approach

With the advent of ultrasound, a diagnostic test that is greater than 90% sensitive in the setting of symptomatic DVT, the use of venography has become extraordinarily uncommon. Magnetic resonance imaging (MRI) has proven extremely sensitive for both acute and chronic DVT, although it is generally not necessary. It is very

reasonable to consider MRI in the setting of suspected DVT when severe edema, trauma, or a plaster cast or other device prevents the effective use of ultrasound.[10] A major limitation of ultrasound is its reduced sensitivity in the setting of asymptomatic DVT. Thus, it is not generally used as a screening test.

Pulmonary Embolism: The Radiographic Approach

Ventilation–Perfusion Scanning

A normal perfusion scan rules out the diagnosis with a high enough degree of certainty that further diagnostic evaluation is almost never necessary.[3] However, low- or intermediate-probability (nondiagnostic) scans are commonly found with PE and in such situations further evaluation with pulmonary arteriography is often appropriate. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) when the clinical suspicion of PE was considered very high, it was present in 96% of patients with high-probability scans, 66% of patients with intermediate-scans, and 40% of patients with low-probability scans.[3] The ventilation-perfusion (VQ) scan is being use much less since the advent of chest CT.

Stable patients with suspected acute PE, nondiagnostic lung scans, and adequate cardiopulmonary reserve (absence of hypotension or severe hypoxemia) may undergo noninvasive lower extremity testing in an attempt to diagnose DVT.[11] A positive compression ultrasound may present the opportunity to treat without further testing. If the ultrasound is negative, pulmonary angiography is an appropriate option.

Pulmonary Arteriography

Pulmonary arteriography remains the accepted gold standard technique for the diagnosis of acute PE, though it is generally not necessary. It is an extremely sensitive, specific, and safe test. Complications of pulmonary arteriography among 1111 patients suspected of PE in the PIOPED included death in 0.5% and major nonfatal complications in 1%.[12] This test is utilized when PE must be diagnosed or excluded, but preliminary testing has been nondiagnostic.

Spiral (Helical) Computed Tomography

Spiral CT scanning can be used for diagnosing both acute and chronic PE and has replaced VQ scanning in most settings at many centers. Some clinical trials have suggested very good sensitivity and specificity but

others have been less favorable. A contrast bolus is required for imaging of the pulmonary vasculature.

In at least one clinical trial, spiral CT has been associated with greater than 95% sensitivity and specificity.[13] More recent and larger trials have suggested a lower sensitivity.[14] A large, prospective Swiss study revealed a sensitivity of 70%, suggesting that a negative CT scan may not absolutely rule out smaller emboli.[14] Preliminary data from a large multicenter trial (PIOPED II) in the U.S. and Canada comparing CT (chest and legs) and VQ scanning suggest that the sensitivity of chest CT is enhanced when the legs are evaluated by CT at the same time (Stein PD, Fowler SE, Goodman LR, et al: Submitted for publication). Spiral CT has the greatest sensitivity and sensitivity for emboli in the main, lobar, or segmental pulmonary arteries. For subsegmental emboli, spiral CT appears less accurate, although the importance of emboli this size have been questioned. The outcome of selected patients with a negative CT in the setting of suspected PE appears to be good in published trials thus far,[15] although no large, prospective outcome trials have been conducted with follow-up in all patients. An advantage of spiral CT over VQ scanning and arteriography includes the ability to define nonvascular structures such as lymphadenopathy, lung tumors, and parenchymal abnormalities as well as pleural and pericardial disease. Another advantage of spiral CT over other diagnostic methods is the rapidity with which a study can be performed. Potential disadvantages of CT include the fact that it is not portable, and patients with significant renal insufficiency cannot be scanned without risk of renal failure.

Magnetic Resonance Imaging

MRI has been utilized to evaluate clinically suspected PE but at present the excellent sensitivity and specificity for the diagnosis of DVT is the main advantage of MRI in this disease process.[16] Disadvantages of MRI include time needed and the potential difficulty in transporting and performing the technique in critically ill patients. Because of the potential to evaluate the legs, lungs, and heart with MRI, there would appear to be tremendous advantages of this technique for suspected acute VTE if the technique could be performed faster and without the potential for claustrophobia (Fig 1).

Echocardiography in Acute Pulmonary Embolism

Echocardiography, which can often be obtained more rapidly than either lung scanning or pulmonary arteriography, may reveal findings which strongly support hemodynamically significant pulmonary em-

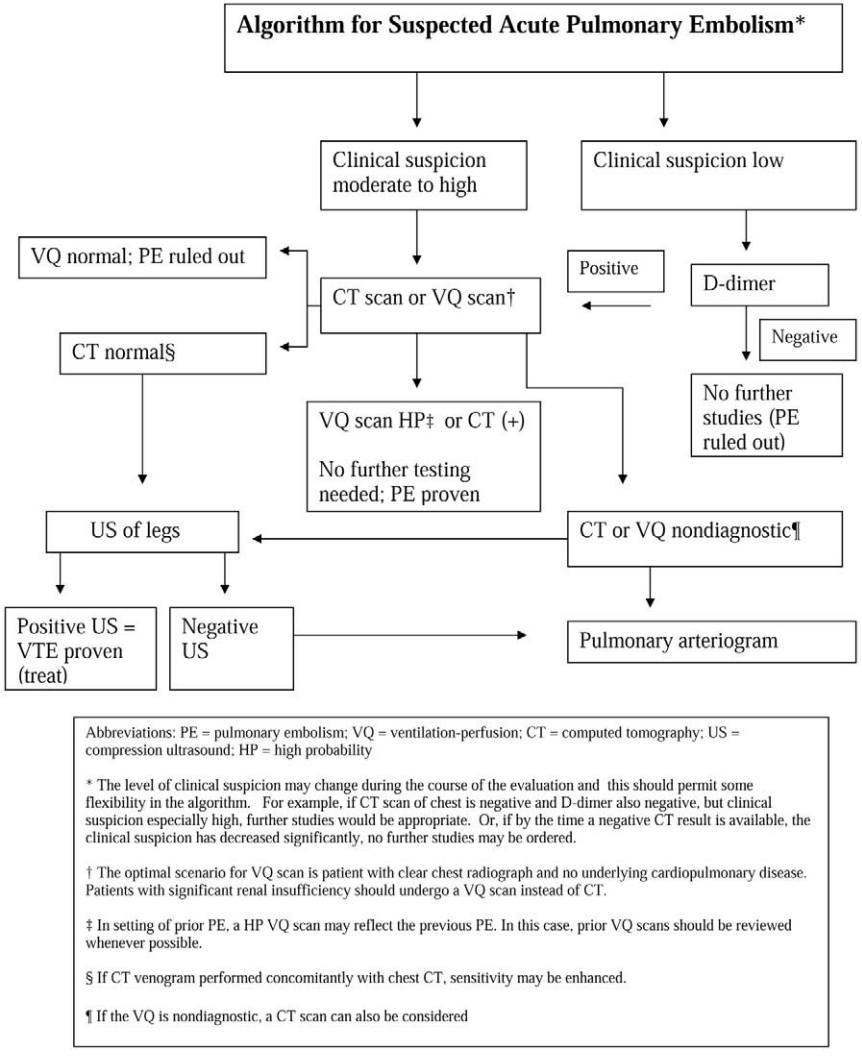

FIG 1.

bolism.[17] Unfortunately, underlying cardiopulmonary disease such as chronic obstructive lung disease renders right ventricular dilation and hypokinesis less specific. With documented acute PE, echocardiographic evidence of right ventricular dysfunction has been suggested as a means by which to determine the need for thrombolytic therapy. While such cases need to be individualized, severe right ventricular dysfunction should lower the threshold for thrombolytic therapy.

Newer algorithms[18] as well as published guidelines[19] suggest that clinicians be afforded a certain degree of flexibility with regard to the diagnostic approach to suspected acute PE.

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Patent Foramen Ovale: The Missing Link between Deep Venous Thrombotic Disease and Embolic Stroke

Michael H. Salinger, MD, FACC, FSCAI and
Ted E. Feldman, MD, FACC, FSCAI

In 1877, Kohnhern, a German anatomist, performed an autopsy on a young woman with a patent foramen ovale (PFO) who had died from a nonhemorrhagic stroke. He hypothesized that a clot passing through the PFO must have caused the patient's demise and thus provided the first description in the medical literature of a paradoxical embolism.[1] In the 128 years since Kohnhern's original description of paradoxical embolism, there has been a great deal of study of the potential association between PFO and stroke. Clinical diagnostic techniques have been developed to permit the antemortum diagnosis of PFO and multiple therapeutic options have been developed and explored. However, despite much scholarly activity, an evidence-based consensus regarding the optimal treatment of patients with PFO and cryptogenic stroke has yet to be developed.

The foramen ovale represents a central location in the intratrial septum where the septum primum and the septum secundum overlap (Fig 1). In utero, these tissues grow to overlap but remain unfused allowing ongoing communication between the right atrium and left atrium. This allows venous blood to return from the placenta to reenter the systemic circulation without traversing the pulmonary circulation. Shortly after birth, the septum primum and septum secumdum fuse and the communication between right and left atrium closes in the majority of cases.[2] Failure of the septum primum and the secundum to fuse results in a PFO.

In a large autopsy study preformed at the Mayo Clinic involving 965 hearts, the incidence of PFO was found to be 27%.[3] Pooled autopsy studies have demonstrated a similar incidence of PFO of 26% with a range of 17 to 35%.[4] Clinically, the antemortum diagnosis of PFO is best made using echocardiography. Transthoracic echocardiography (TTE)

Dis Mon 2005;51:94-103
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.003

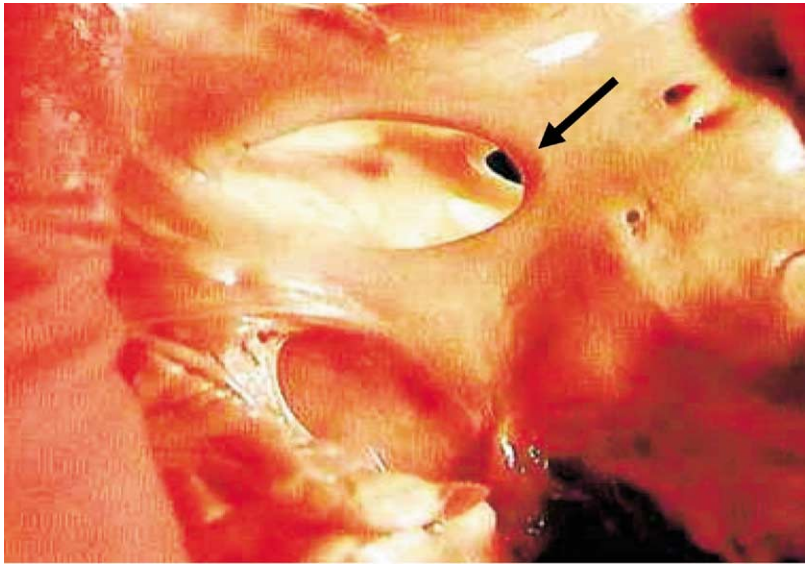

FIG 1. Autopsy specimen demonstrating patent foramen ovale (single arrow) as viewed from the right atrial side. Left-sided septum primum is seen within the foreman ovale and right-sided septum secundum (underlying the arrow) is seen. Photo courtesy of NMT Medical.

has limited ability to detect PFO and the incidence of PFO detected by TTE in large active laboratories has been 10 to 18%. Properly performed, transesophageal echocardiography (TEE) in large active laboratories has detected PFO in 18 to 33% of patients studied. The incidence of PFO by TEE very closely approximates the incidence of PFO in pooled autopsy data and has lead to the position that a properly preformed TEE is the clinical gold standard for antemortum detection of PFO. To be properly preformed, the TEE study should include Doppler flow interrogation and imaging with intravenous injection of agitated saline or echo imaging contrast agent during a Valsalva maneuver or with external abdominal compression to demonstrate right-to-left flow across the intraatrial septum.[5] TEE also provides potentially import information regarding atrial septal morphology, the presence of an atrial septal aneurysm, and the presence or absence of intraatrial thrombus or masses. The absence of the demonstration of a PFO on transthoracic imaging (TTE) does not exclude the potential of a PFO.

More recently, intracardiac echo has been used as both a diagnostic imaging modality as well as a direct transcatheter therapeutic maneuver. Less invasive screening has been recently advocated using IV contrast and either transcranial Doppler (TCD) imaging or carotid duplex scan-

ning.[6] Intravenous bubble contrast is administered, and early appearance of a Doppler signal in the cerebral circulation demonstrates the presence of a shunt. A positive screen would establish the presence of a right-to-left shunt and trigger further evaluation with TEE. The specific sensitivity and specificity of this approach appears quite promising.[7]

Over the years, multiple studies have demonstrated a statistically significant relationship between cryptogenic stroke, that is to say, stroke without any other detectable cause, and the presence of a PFO. This relationship is most apparent when evaluating patients under 55 years of age. In 2000, Overell and coworkers published a meta-analysis of nine studies involving over 1000 patients under the age of 55 and found a very positive association between PFO in patients with cryptogenic stroke with an odds ratio of 3.10.[8] In individual studies, the incidence of PFO in cryptogenic stroke patients has been demonstrated to be statistically different from non-stroke populations with a 3- to almost 10-fold increase in the incidence of PFO in cryptogenic stroke populations as compared with controls. The incidence of PFO in cryptogenic stroke populations appears to approximate 50%. Perhaps the most dramatic demonstration of the potential relationship between venous thromboembolic disease, PFO, and stroke have come from the operating room where thrombus has been directly visualized traversing a PFO (Fig 2A). Although less dramatic, equally incriminating evidence has come from the autopsy suite where thrombus has been observed within PFOs (Fig 2B). An alternative hypothesis for the origin of these thrombi is in situ formation within the PFO.

Mas and coworkers described a higher risk for stroke among patients with PFO and atrial septal aneurysm (ASA). In a study of 581 patients aged 18 to 55 years with ischemic stroke of unknown origin, the risk of recurrent stroke over a 4-year period was 15.2% versus 4.2% with neither PFO nor aneurysm.[9] There were no recurrences among patients with ASA alone.

Determining what is appropriate treatment for PFO associated with cryptogenic is of importance, given that American Stroke Association statistics estimate one-half million new ischemic strokes occur annually in the United States.[10] Accepting the data that approximately one-third of ischemic strokes are cryptogenic and that approximately one-half of cryptogenic strokes are associated with PFO, there could be an estimated 80,000 cases of new PFO-related cryptogenic stroke annually in the United States alone. Unfortunately, significant controversy persists regarding how to treat this large and complex population.

There are limited data regarding the natural history of PFO-associated

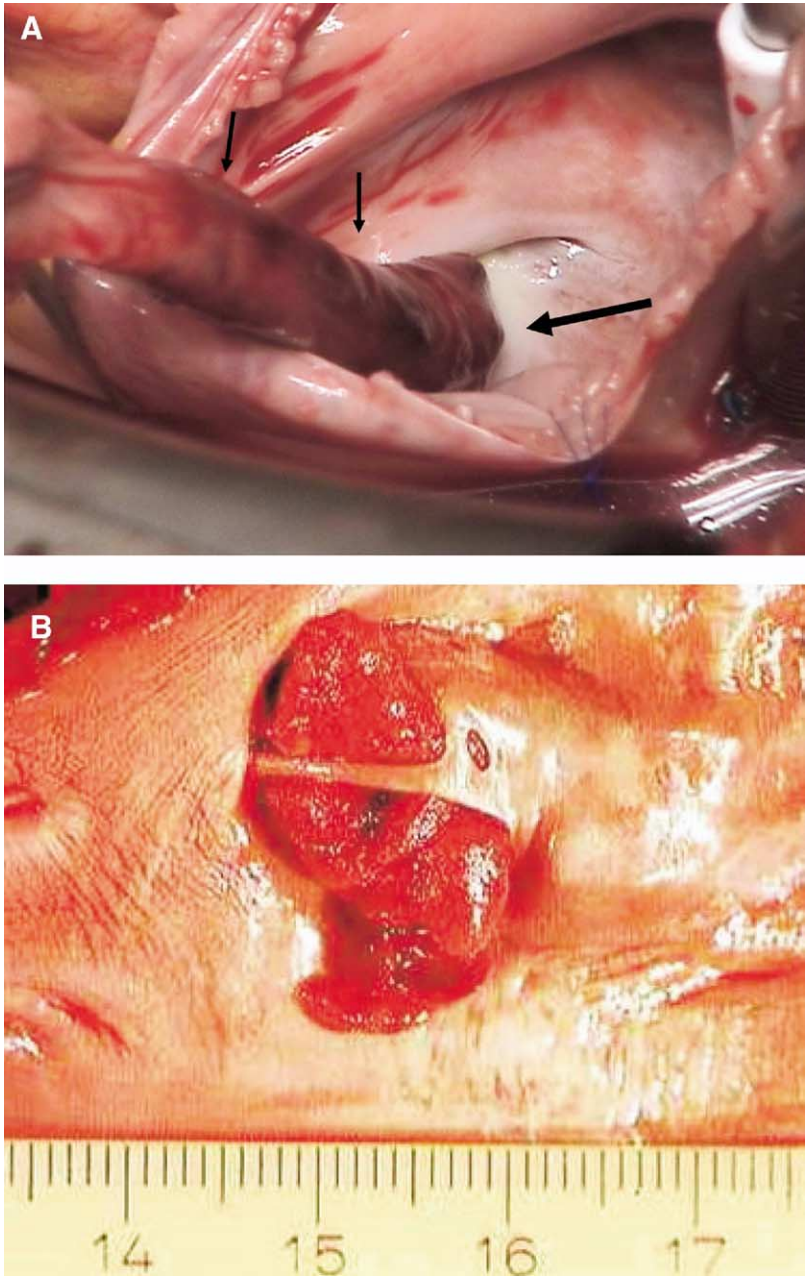

FIG 2. (A) Intraoperative photograph of intraatrial septum as viewed from the right atrium demonstrating large "worm-like" thrombus (small arrows) traversing patent foramen ovale (large arrow). Photo courtesy of AGA Medical. (B) Autopsy specimen demonstrating thrombus within patent foramen ovale. Photo courtesy of NMT Medical.

cryptogenic stroke. In one small study, 33 patients with apparent PFO-related paradoxical embolism were followed 18 months without medical or surgical therapy. The annualized 1-year recurrent event rate in this small group was found to be 16%.[11] Data regarding surgical therapy are also limited and suggest surgical closure of the PFO is an imperfect therapy. One of the larger studies of surgical therapy involved 92 patients and reported a 1-year recurrent event-free survival rate of 92% and a 2-year event-free survival of 83%.[12]

Studies of medical therapy for PFO-related cryptogenic stroke have been confounded by multiple limitations including heterogeneous patient populations, multiple treatment strategies, small study size, retrospective analysis, and the absence of control groups. One of the largest randomized studies of medial therapy for ischemic stroke of all etiology was the Warfarin Aspirin Randomized Recurrent Stroke Study (WARRS). This study involved over 2160 patients ages 30 to 85 with ischemic stroke of all etiologies randomized to treatment with either aspirin or coumadin with an INR goal of 1.4 to 2.8. At 2 years, recurrent stroke rates were not statistically significantly different between the two groups with a 17.8% recurrent event rate in the aspirin group and a 16.0% event rate in the warfarin group.[13]

The PFO in Cryptogenic Stroke Study (PICSS) examined a subset of WARRS patients who underwent TEE and were found to have a PFO. In this subset of 203 WARRS patients, recurrent event rates at 2 years in the warfarin versus aspirin cohorts were not statistically different with a 16.5% recurrent stroke rate in the warfarin group and 13.2% recurrent event rate in the aspirin group ($P = 0.65$).[14] While some investigators have reported that PFOs with "high-risk" morphologic features such as a large septal aneurysm or the presence shunting across the PFO in the absence of provocation may predispose patients to increased risk of recurrent events,[15] the PICSS investigators found atrial septal morphology and resting physiology did not impart an increased risk of recurrent events in patients medically managed with either aspirin or warfarin.

In the years since the inception of studies of medical therapy for PFO-related stroke, we have seen the technological advancement and refinement of percutaneous techniques for PFO and atrial septal defect closure which were first pioneered over 25 years ago.[16] While multiple devices have been designed and developed both in Europe and in the United States, currently there are two basic device designs which are available to interventional cardiologists in the United States. In 2000, the fabric-covered umbrella device from NMT Medical, Inc. (Boston, MA) known as the CardioSeal® received a Humanitarian Device Exception

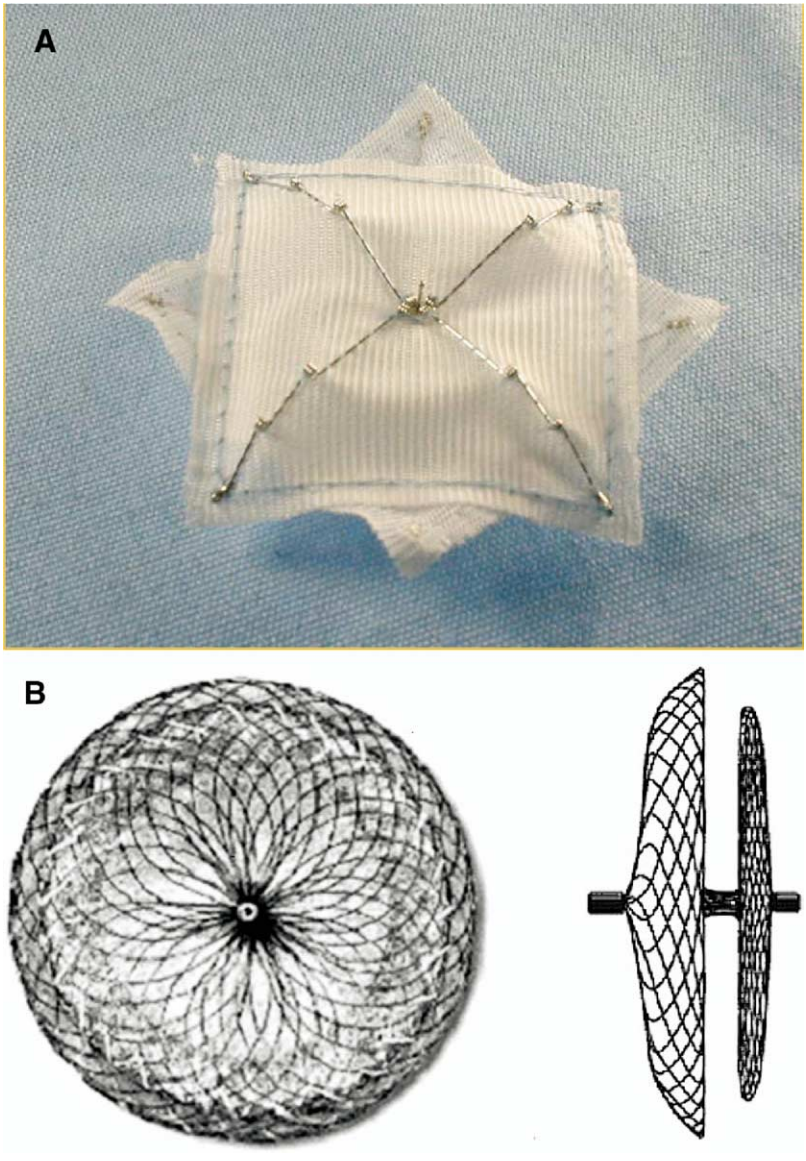

FIG 3. (A) NMT CardioSeal FPO closure device demonstrating fabric-covered "double umbrella" design. Courtesy NMT Medical. (B) AGA Medical Amplatzer PFO device demonstrating fabric-enclosed wire mesh design. Courtesy AGA Medical.

(HDE) for PFO closure from the Food and Drug Administration (FDA) (Fig 3A). In 2002, the nitinol wire mesh device from AGA Medical Corp. (Golden Valley, MN) known as the Amplatzer® PFO device received a

similar HDE from the FDA (Fig 3B). Both of these devices are placed percutaneously via a transfemoral venous approach.

The relative ease and efficacy of the percutaneous approaches for PFO closure have caused a rapid adoption of these procedures.[17] The available PFO closure devices are implanted in a cardiac catheterization suite in an awake patient using local femoral anesthesia. The route of delivery is by femoral venous puncture. No arterial puncture is typically used, so the incidence of vascular complications is low. The procedures are often guided by echocardiography. While transesophageal echocardiogram was commonly used during the early development of these approaches, intracardiac echocardiography, also delivered via femoral venous puncture, is now common in most catheterization laboratories performing percutaneous closure. The procedure generally takes less than 1 hour and can be performed on an outpatient or one-night-stay basis. The dramatic change in the ability to achieve closure of these defects compared to surgical approaches via sternotomy or thoracotomy has created a great deal of interest among patients with PFO to seek closure.

The efficacy of the percutaneous approaches has been demonstrated in numerous trials. The vast majority of defects are closed completely following device implantation and the devices are overgrown by tissue within a few months. Patients are typically treated with aspirin or aspirin and clopidogrel for 6 months after closure devices are implanted. Endocarditis prophylaxis is generally recommended for 6 months as well. Major complications occur in about 1% of cases and include access site bleeding complications, thromboembolism or stroke, and device embolization.[18] In extremely rare cases with the AGA Medical device there is erosion of the device through the free wall of the atria.[19] Cases of device thrombus have been demonstrated and have responded to therapy with coumadin or intravenous heparin, but a few have required surgical explantation.[20]

The FDA HDE is a process by which the CardioSeal PFO and Amplatzer PFO devices became available under limited and highly restrictive conditions which require that a patient experience a cerebral event despite treatment resulting in a therapeutic INR. An HDE is not an unrestricted approval and "off-label" PFO-labeled device use is not permitted.[21] More often than not the patient would have suffered an initial event off therapy and then would need to experience a second event while on coumadin to meet the requirements of the HDE. The HDE approval limits therapy to patients with recurrent stroke. Many practitioners and certainly patients with PFO and stroke do not wish to wait for a recurrent event prior to closure of the defect. Randomized trial evidence to justify

this practice is lacking. Randomized trials to compare PFO closure using percutaneous devices with medical therapy among patients who have had a single stroke or transient ischemic attack are underway.

Interestingly, the NMT ventricular septal defect (VSD) device differs from their PFO device only by catalog number and has unrestricted FDA approval. The AGA atrial septal defect (ASD) device is very similar to their PFO device. The "off-label" use of VSD and ASD closure devices for PFO closure appears to be feasible and is a growing practice in United States. This practice may have a significant negative impact on recruitment for the ongoing FDA monitored prospective randomized trials of medical therapy versus percutaneous PFO closure, which include the RESPECT PFO trial (AGA Medical), the CLOSURE I trial (NMT Medical), and the CARDIASTAR Trial (Cardia, Inc.).[22]

The absence of data from randomized trials of medical therapy versus device closure for treatment of PFO in patients with cryptogenic stroke is stressed in the 2004 Report of the Quality Standards Subcommittee of the American Academy of Neurology entitled "Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm."[23] Multiple nonrandomized evaluations of medical therapy and device therapy have appeared in the literature. In the absence of data from randomized trials, Khairy and colleagues have conducted a comprehensive systematic review of the literature.[17] This review screened 236 studies and ultimately analyzed 16 trials involving 2250 patients. While acknowledging the limitations of systematic retrospective review, the authors found a 1-year recurrent neurologic thromboembolic rate of 0 to 4.9% in the transcatheter intervention group with a 1.5% incidence of major complications, while medical therapy was associated with a 1-year recurrence rate of 3.8 to 12.0%. In January 2004 Landzberg published his "Indications for the closure of patent foramen ovale" citing pooled data with an adjusted 2.7% recurrent stroke/TIA incidence in the device group and a 7.1% adjusted recurrent stroke/TIA event rate at 1 year in the medical group ($P < 0.0001$) adding weight to the perception that percutaneous closure may be superior to medical therapy.[24]

It is our belief that PFO does indeed represent the "missing link" between deep venous thrombotic disease and stroke. Percutaneous closure is a recognized and FDA-cleared therapy for PFO patients who have recurrent events with a therapeutic INR. Attempted secondary prevention of recurrent cerebrovascular events using percutaneous closure in patients who have not failed medical therapy remains controversial and demonstration of the relative efficacy of medical therapy versus percutaneous

PFO device closure awaits the completion of ongoing prospective randomized trials.

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The Treatment of Deep Venous Thrombosis, Including the Newer Agents

John E. Rectenwald, MD, and
Thomas W. Wakefield, MD

Introduction

Barritt and Jordan performed the first and only randomized trial of treatment of venous thromboembolism [VTE—deep venous thrombosis (DVT) and pulmonary embolism (PE)] with unfractionated heparin sodium (UFH) and an oral vitamin K antagonist at Bristol Royal Infirmary in 1957.[1] This study reported a 26% mortality rate (5 of 19 in the control arm) for untreated patients with VTE. Today, the mortality associated with untreated PE is reported as approximately 30%, a figure that has not changed since the publication of this landmark study.

The study by Barritt and Jordan was quickly incorporated into standard practice for treatment of VTE with anticoagulation. Further, the improved outcomes for patients with PE were soon extrapolated to patients for treatment of uncomplicated DVT alone.

Incidence, Risk Factors, and Categories

DVT affects more than 250,000 patients per year and the complications of acute DVT, PE, and postthrombotic syndrome are the most common cause of preventable hospital death and substantial long-term morbidity. PE has been estimated to occur in at least 200,000 persons annually, being the cause of death in over 15,000, although other estimates suggest that PE may actually afflict 600,000 cases per year. In addition, approximately 50% of patients with significant DVT develop chronic venous insufficiency from the associated valvular and venous wall damage that results from DVT. Given these estimates and the fact that prevalence of DVT and PE has not changed significantly over the last 25 years, DVT and PE remain a significant problem in clinical practice today. New understand-

Dis Mon 2005;51:104-111
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.004

ing concerning the genetic and acquired risk factors for DVT has been attained and is discussed in depth elsewhere.

Most DVT affect the lower limb and the popliteal, femoral, or iliac veins. Presenting symptoms include unilateral limb pain and swelling, but DVTs are sometimes silent, with a first manifestation as PE. A recent study of 5451 patients with ultrasound confirmed DVT revealed the five most common comorbidities to be surgery within 3 months, immobility within 30 days, cancer, obesity, and, of interest, hypertension.[2]

Treatment of DVT

As discovered in the Barritt and Jordan study, the primary treatment of VTE is systemic anticoagulation, which reduces the risk of propagation of thrombus, PE, the extension of VTE, and the recurrence of venous thrombosis. After the diagnosis of VTE, immediate anticoagulation should be undertaken if not contraindicated.

Traditionally, systemic intravenous UFH has been undertaken for 5 days, during which time oral anticoagulation with warfarin is instituted. Because of bleeding risks of UFH, along with the need for systemic administration, low-molecular-weight heparin (LMWH) has been advanced as primary therapy. In summary of multiple studies and meta-analyses, LMWHs are at least equivalent to standard unfractionated heparin (if not slightly superior) regarding thrombus recurrence, with a lower risk for major hemorrhage and even an improvement in mortality rate.[3] LMWHs are derived from the lower molecular weight range of standard heparin with greater anti-factor Xa activity and less direct thrombin inhibition. The advantages of LMWHs include less bleeding, less antiplatelet activity, lower incidence of heparin-induced thrombocytopenia, less interference with protein C and complement activation, and a lower risk for osteoporosis and alopecia. As LMWHs can be administered subcutaneously and are weight-based dosed, they may be given as an outpatient and do not require frequent monitoring with anti-factor Xa levels except in certain circumstances such as renal insufficiency, morbid obesity, and occasionally during pregnancy.[4] Subcutaneous, rather than intravenous, treatment has the potential advantage of earlier patient ambulation and earlier discharge to home.

Oral anticoagulation with warfarin should be started only after heparinization is therapeutic to prevent warfarin-induced skin necrosis. The goal for warfarin is an international normalized ratio (INR) between 2.0 to 3.0. The recommended duration of anticoagulation after a first episode of DVT in patients with reversible risk factors is 3 to 6 months. For patients with idiopathic DVT the recommended treatment duration is

longer.[5] After a second episode of DVT, the usual recommendation is lifelong warfarin unless there are other mitigating factors. Recurrent DVT is increased significantly with homozygous Factor V Leiden and prothrombin 20210A mutation, protein C/S deficiency, antithrombin deficiency, antiphospholipid antibodies, and cancer. Heterozygous Factor V Leiden and prothrombin 20210A do not carry the same high risk of recurrence and the length of oral anticoagulation may be shortened. However, combined heterozygous deficiency states likely are additive. Calf thrombi have been traditionally treated with 6 weeks of warfarin; however, recent studies have questioned this practice and many authors have argued for a longer period of treatment. This is supported by the finding that many patients with isolated calf vein thrombosis have a higher incidence of presence of a prothrombotic states[6] and many suffer the long-term sequelae of chronic venous insufficiency with as many as 23% of patients having symptoms at 1 year.[7] In addition, a study of 75 patients with isolated calf vein thrombosis showed that the calf thrombus propagated proximally in 32% and that 5% suffered PE.[8]

A recent multicenter trial suggested that, for idiopathic DVT, low-dose warfarin (INR 1.5 to 2.0) is statistically superior to placebo over a 4-year follow-up (64% risk reduction for recurrent DVT after the completion of an initial 6 months of standard warfarin therapy).[9] A second study suggested that full-dose warfarin (INR 2.0 to 3.0) is superior to low-dose warfarin in these same types of patients without a difference in bleeding.[10]

The most common complications of anticoagulation include bleeding and heparin-induced thrombocytopenia (HIT). The bleeding risk has been suggested to be approximately 10% over the first 5 days. With warfarin at an INR of 2 to 3, the incidence of major bleeding is approximately 2 to 4%/year.[11] HIT occurs in 0.6 to 30% of patients in whom heparin is administered. While morbidity and mortality have been high, early diagnosis and appropriate treatment have decreased rates to 6 and 0%, respectively.[12] HIT, caused by a heparin-dependent antibody immunoglobulin G (IgG), which binds to platelets and induces them to aggregate when exposed to heparin, usually begins 3 to 14 days after heparin administration.[13] Both bovine and porcine heparin as well as LMWH has been associated with HIT but the incidence with LMWH is much less. Both arterial and venous thromboses have been reported, and even small exposures to heparin have been known to cause the syndrome.[14] The diagnosis should be suspected in a patient who experiences a 50% drop in platelet count, or when the platelet count falls below 100,000/μl during heparin therapy, or in any patient who experiences thrombosis (particu-

larly in unusual sites) during heparin administration.[15,16] The cessation of heparin is the most important step in treatment. Warfarin is contraindicated in this condition until an adequate alternative anticoagulant becomes effective. The direct thrombin inhibitors hirudin (Lepirudin) and argatroban are the treatment of choice as these agents show no cross-reactivity to heparin antibodies.[17] LMWH has too high an incidence of cross-reactivity to be used in HIT without being tested in vitro.

In summary, the general consensus for treatment of patients with objectively confirmed DVT is treatment with short-term anticoagulation with IV UFH, SC UFH, or SC LHWH of at least 5-days duration. Warfarin may be started on the same day as heparin. Heparin should be discontinued when the INR is stable and greater than 2.0 (generally 2 days in a row). In patients with a high clinical suspicion of PE, heparin should be started while awaiting objective confirmation of the presence of PE, while for DVT, treatment can usually await confirmation of the diagnosis. Once or twice daily treatment of DVT with LMWH is preferred over UFH, although IV UFH is recommended over LMWH in patients with severe renal failure (creatinine clearance <30). If LMWH is used, the dose must be adjusted appropriately.[5]

Special Features of LMWH

Patients treated with LMWH become therapeutic quickly. Although not currently FDA approved for use in treatment of DVT in cancer patients, LMWH such as tenzaparin and oxzaparin may also improve survival in cancer patients by decreasing tumor angiogenesis and interfering with tumor thrombus formation that effects tumor metastasis.[18] The safety of LMWH compared to warfarin has led to a consideration of the long-term use of LMWH as a replacement for oral vitamin K antagonists. Although in general there is absence of definitive evidence of superiority for LMWH, rates of recanalization have been reported to be higher in certain venous segments (common femoral vein, femoral vein, and popliteal vein) using LMWH versus traditional oral agents.[19] Additionally the use of dalteparin has been found to be better than warfarin in certain cancer patients when used for 6 months without differences in major bleeding.[20]

The use of once-a-day as compared to twice-a-day LMWH dosing has been assessed in a meta-analysis of greater than1500 patients with VTE.[21] There was a nonsignificant difference in the incidence of recent thromboembolism, thrombosis size, hemorrhagic events, and mortality, suggesting that the more convenient once-daily regimen is adequate for treatment.

Finally, although LMWH is dosed by weight, it would be more

convenient if it could be based on anti-factor Xa units. A LMWH preparation available in Europe (Certoparin) has been given independent of patient weight and found to be equivalent to standard intravenous heparin in its efficacy.[22] This suggests that such fixed-dose, weight-independent dosing is possible and requires further study.

New Treatments for DVT

Two new therapeutic agents have demonstrated the promise of greater efficacy with less bleeding risk in both VTE treatment and prophylaxis. These include direct thrombin inhibitors and specific factor Xa inhibitors. The direct thrombin inhibitor, Ximelagatran/Melagatran, can be taken orally and may be an alternative to warfarin. Ximelagatran offers no increase in bleeding potential compared to warfarin, without the need for frequent monitoring. In a large prospective study comparing oral Ximelagatran (which is metabolized to the active Melagatran) to placebo for 18 additional months after 6 months of standard anticoagulant treatment for DVT in 1223 patients, the recurrent DVT/PE rate was significantly reduced from approximately 12.6 to 2.8%.[23] Major and minor bleeding events were equivalent at 23.9 and 21.0%. Likewise, this agent has been found effective in the prophylaxis of DVT in orthopedic surgery patients. The only worrisome abnormality is an increase in liver function tests that appears to normalize on its own. It is because of this alteration in liver function tests that Ximelagatran is currently not FDA approved in the U.S.

The specific factor Xa inhibitor pentasaccharide (Fondaparinux) potentiates approximately 300 times the neutralization of factor Xa by antithrombin, without inactivating thrombin. The total lack of an association of the drug with HIT is an advantage when considering treatment of DVT or VTE in cancer patients or patients who are critically ill. In addition, the 17-hour half-life makes once daily dosing of Fondaparinux possible.

Large prospective randomized studies for both DVT and PE treatment (MATISSE trial) have also been conducted.[24,25] For DVT, with 2205 patients (>30% outpatients) treated with 7 to 10 mg of Fondaparinux subcutaneously daily, the recurrent DVT rate/major hemorrhage rate for pentasaccharide (3.9%/1.1%) was equivalent compared to enoxaparin (4.1%/1.2%). For PE, with 2213 patients (with >15% outpatients), recurrent PE/major hemorrhage rate for pentasaccharide (3.8%/1.3%) was again equivalent to standard unfractionated heparin (5%/1.1%). Mortality rates were equal. This suggests that for treatment of VTE, Fondaparinux

is at least equivalent to standard therapy and certainly more convenient to use, since the drug is dosed independent of laboratory monitoring.

Fondaparinux has also been studied in prophylaxis of DVT. In orthopedic surgical procedures including hip fracture, hip replacement, and knee reconstructive surgery at a dose of 2.5 mg subcutaneously begun 6 hours after surgery, this agent has also shown superiority to the best currently available DVT prophylaxis, enoxaparin at either 40 mg subcutaneously once daily beginning preoperatively or 30 mg twice daily beginning postoperatively and is associated with a risk reduction of 55%.[26] This suggests that for treatment of VTE, Fondaparinux is again at least equivalent to standard therapy and certainly more convenient to use, since the drug is dosed independent of laboratory monitoring.

For VTE prophylaxis in 2297 abdominal surgery patients (70% for cancer resection), the incidence of DVT was lower in patients who received Fondaparinux than patients receiving dalteparin. The incidence of DVT in patients who were treated with 2.5 mg of Fondaparinux daily was 4.6% versus 6.1% (at 30 days) in patients that were treated with 2500 units of dalteparin preoperatively, or started with 2500 units immediately postoperatively and then given 5000 units daily. There was no difference between groups in relation to major bleeding complications. In the group of patients with cancer, the incidence of DVT was significantly reduced (4.6% in the Fondaparinux group versus 7.7% in the dalteparin group).[27]

For extended prophylaxis in 656 patients undergoing hip fracture surgery, after 7 days of Fondaparinux at 2.5 mg per day, patients were then randomized to either Fondaparinux or placebo subcutaneously for the following 3 weeks. At 1 month, Fondaparinux reduced the rate of DVT from 30% in the placebo group to 1.4% ($P < 0.001$).[28]

Fondaparinux has also been evaluated for prophylaxis in the general medical population. In this study, 2.5 mg of Fondaparinux started within 24 hours of hospital admission and continued for a total 6 to 14 days decreased the risk of VTE from 10.5% in the placebo group to 5.6% in the treatment group ($P = 0.029$). Fatal PE was also significantly reduced. Major bleeding was not different from placebo and there was a trend to reduction of mortality with Fondaparinux treatment.[29]

Another related compound, idraparinux, has also been investigated. This compound has a long 130-hour half-life, allowing longer intervals between dosing. Compared to oral anticoagulation, idraparinux at a dose of 2.5 mg subcutaneously per week was as effective as warfarin for secondary prevention of DVT and was not associated with an increase in major bleeding.[30]

Currently, Fondaparinux is FDA approved for prophylaxis for total hip and total knee replacement, hip fracture, and for the long-term prophylaxis after treatment of hip fracture. It is also approved for DVT treatment, as well as PE treatment without DVT.

These two classes of agents alone, direct thrombin inhibitors and specific factor Xa inhibitors, in addition to others currently being investigated, will likely revolutionize the treatment and prophylaxis of VTE in the near future.

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Why Warfarin and Heparin Need to Overlap When Treating Acute Venous Thromboembolism

Ann K. Wittkowsky, PharmD, CACP, FASHP

Introduction

The American College of Chest Physicians Conference on Antithrombotic Therapy provides nationally recognized, graded recommendations for the treatment of venous thromboembolic disease (VTE) based on a thorough assessment of available evidence.[1] The most recent guidelines recommend that VTE be treated initially with either unfractionated heparin (UFH) or a low molecular weight heparin (LMWH) and that warfarin be initiated simultaneously.[2] The UFH or LMWH should be continued for a minimum of 5 days and discontinued when the International Normalized Ratio (INR) is stable and at or above 2.0. The recommendation that heparins and warfarin overlap for a 5-day period is based on pharmacokinetic, pharmacologic, pathophysiologic, and clinical evidence.

Pharmacokinetic Evidence

Warfarin, a vitamin K antagonist, exerts its anticoagulant effect by interfering with the hepatic synthesis of vitamin K dependent clotting factors II, VII, IX, and X, as well as proteins C and S.[3] The onset of effect of warfarin and the time to therapeutic effect are partially dependent on its pharmacokinetic properties. The average elimination half-life of S-warfarin, the more potent of the two optical isomers of warfarin, is approximately 30 hours.[4] According to standard pharmacokinetic principals, three to four elimination half-lives are required to reach steady-state plasma drug concentrations.[5] Thus, warfarin must be dosed daily for 4 to 5 days to reach steady state.

Pharmacologic Evidence

Once warfarin therapy is initiated, synthesis of vitamin K dependent coagulation factors is inhibited, but previously formed clotting factors

Dis Mon 2005;51:112-115
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.005

TABLE 1. Elimination half-lives of vitamin K dependent coagulation proteins

Coagulation factors	
Factor II	42–72 hours
Factor VII	4–6 hours
Factor IX	21–30 hours
Factor X	27–48 hours
Anticoagulant proteins	
Protein C	9 hours
Protein S	60 hours

also must be eliminated at rates that correspond with their own elimination half-lives (Table 1).[6] In an evaluation of rates of decline of vitamin K dependent proteins following typical initiation dosing of warfarin, factor VII, with the shortest elimination half-life, was eliminated most rapidly, while the other vitamin K dependent clotting factors declined gradually.[7] Thus, early elevations in the INR correspond with reductions in factor VII concentrations.[8] In an experimental animal model of thrombosis, selective suppression of factor VII and of factor IX was not adequate to protect against tissue-factor-induced intravascular coagulation, while selective suppression of factors II and X prevented thrombosis.[9] Effective elimination of factor II and factor X to 50% of their initial concentrations requires one half-life, and to 25% of their initial concentrations requires two half-lives. Based on the extended elimination time of factor II, this process likely requires 4 to 5 days to occur.

Pathophysiologic Evidence

Genetic deficiencies of protein C, a naturally occurring anticoagulant, are associated with hypercoagulability.[10] Like factor VII, protein C has a relatively short elimination half-life (Table 1). When warfarin was initiated with 10-mg loading doses in 49 patients, with subsequent dosing guided by INR response, protein C and factor VII levels declined rapidly, while factor II levels declined gradually.[11] At 36 hours, factor II levels were 74% of baseline, while factor VII and protein C levels were approximately 30% of baseline. This relative protein C deficiency, characterized by near-normal factor II levels and markedly reduced protein C levels, could result in a hypercoagulable state.

Clinical Evidence

The pharmacokinetic properties and pharmacologic characteristics of warfarin suggest that an adequate pharmacodynamic effect is not achieved for 4 to 5 days after the initiation of dosing, and pathophysio-

logic evidence suggests that early anticoagulation with warfarin may induce a hypercoagulable state. Further clinical evidence has confirmed the inherent risks associated with this delayed onset of effect in patients with acute venous thromboembolism. In a double-blinded clinical trial, 120 consecutive patients with proximal vein thrombosis were randomized to receive continuous infusion heparin adjusted to maintain the activated partial thromboplastin time at 60 to 90 seconds, and acenocoumarol, a coumarin derivative, dosed to maintain the INR between 2 and 3, or to the coumarin alone with an intravenous placebo.[12] The injectable agent was continued for a minimum of 7 days and was discontinued when two consecutive INRs were within the therapeutic range. The coumarin was continued for 3 months, and the patients were followed for a total of 6 months.

The study was terminated early due to excessive symptomatic events in the patients treated without overlapping heparin. During the 6-month study period, symptomatic extension or recurrence of venous thrombosis, confirmed by objective testing, occurred in 20% of the patients treated with acenocoumarol alone, compared to only 6.7% of patients treated with heparin and acenocoumarol ($P = 0.058$). This clinical evidence confirms that overlap with heparin or LMWH is required while the therapeutic effect of warfarin is gradually reached.

Summary

The pharmacokinetic characteristics of warfarin, and the time delay in achieving an antithrombotic effect based on the elimination half-lives of the vitamin K dependent clotting factors, suggest the need for overlap with heparin during initial warfarin dosing. The potential for the development of relative protein C deficiency provides further justification for heparin overlap. Clinical evidence from a randomized trial of a coumarin alone compared to a coumarin plus heparin for the initial management of acute VTE has confirmed the need for heparin overlap during the initiation of oral anticoagulation. This combined therapy is necessary to prevent recurrent thrombosis.

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Management of Pulmonary Embolism in 2005

Bruce L. Davidson, MD, MPH, and
Witold Z. Tomkowski, MD

Pulmonary embolism is a common, life-threatening, yet still misdiagnosed and mistreated disease. Many aspects of the management of pulmonary embolism have changed significantly in recent years, while others have not. This review will summarize key aspects of diagnosis and treatment. Readers are referred to key texts and longer reviews for specific areas of interest.

Diagnosis

It is critical to understand that the vast majority of diagnostic studies have included symptomatic outpatients rather than inpatients. Inpatients have increased disease burden and more complicated illnesses. Since predictive values of diagnostic tests depend to a great degree on the preexisting probability of having a pulmonary embolism and this can be more difficult to estimate in complicated inpatients, it is understandable that the predictive values of the tests may be lower for inpatients. In outpatients, the incidence of a proven pulmonary embolism with a "negative" D-dimer accompanied by a "low clinical probability" is $\leq$1% h.[1] Two warnings pertain to using this information: This does not apply to borderline D-dimer values, and inexperienced physicians should use a clinical scoring system to arrive at their estimate of clinical probability. In outpatients, a management study of suspected pulmonary embolism has shown that no treatment is needed if the following three conditions pertain: (a) clinical suspicion is low or moderate; (b) duplex ultrasound of both proximal lower extremities (including the popliteal vein) is normal; and (c) the contrast helical CT pulmonary angiogram is truly negative (a CT that shows isolated subsegmental clot is considered indeterminate, not negative, and not positive).[2] If clinical suspicion is high, further testing is required.

Dis Mon 2005;51:116-123
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.006

The usefulness of D-dimer testing remains controversial in inpatients, in part due to a high percentage of "positive" D-dimer values among them consequent to a broad spectrum of diseases (other than pulmonary embolism) and procedures related to the hospitalization. Moreover, for inpatients, a negative D-dimer reduces suspicion but its sensitivity is only 89%, unsatisfactory to exclude pulmonary embolism.[3] If the helical contrast CT angiogram is negative and ultrasound is negative, there is still a 5% false-negative rate for inpatients.[2] There are no convincing data regarding a negative CT alone for inpatients. Accordingly, CT and D-dimer evidence may add information but conventional pulmonary arteriography may still be required to make a secure diagnosis. In its absence, a "clinical" decision to treat (and suspend treatment, if contraindications supervene) may be required.

Multislice CT for confirmation and exclusion of pulmonary embolism appears to be more promising than prior CT technology but remains under investigation. The identification by CT of other pathology in the chest that might explain symptoms, while considered by some authors to help exclude pulmonary embolism, is not persuasive to us, since occult pulmonary embolism can accompany many of these diseases (pneumonia, cancer, etc.)

Oxygenation

A pulse oximeter should be employed on every encounter with the patient and supplementary oxygen should be supplied as needed to keep the O_2 saturation $>92\%$. Patients should be checked with activity (eg, stair-climbing), since most will do such minimal activity as outpatients. When supplemental oxygen is no longer required by these criteria, it may be discontinued. Supplemental oxygen, especially in patients with overload of the right ventricle and coexisting hypoxemia, is itself a vasodilator which can decrease pulmonary artery pressure and pulmonary vascular resistance, which has been pathologically elevated by pulmonary embolism.

Hemoptysis

Hemoptysis may be safely ignored most of the time—it is usually attributable to pulmonary infarction. Under these circumstances, it is not a contraindication to anticoagulation and patients may be reassured that it will stop soon. In rare instances, when persistent or of large volume, it may be a signal of an undiscovered bronchogenic tumor that warrants bronchoscopy or CT of the chest. Primary lung cancer or pulmonary metastases of various tumors can coexist with pulmonary embolism.

Pleuritic Pain

Pleuritic-type pain is common with pulmonary embolism. It is easily relieved by indomethacin,[4] which we dose at 50 mg every 6 to 8 h, or perhaps with another nonsteroidal antiinflammatory drug prescribed at appropriate dosage and intervals. Some physicians administer 30 ml antacid with each dose to prevent dyspeptic distress. Pleuritic-type pain is reduced within 24 h after this regimen and usually eliminated within 48 h. There is no need for concern regarding the possibility of worsening bleeding risk due to possible platelet inhibition by such drugs. Moreover, there is usually no need for narcotics with attendant constipation and sleepiness preventing ambulation.

Pleural Effusion

Pleural effusion is common, usually unilateral, and exudate, and is bloody a little less than half the time if it is sampled, and occupies $<50\%$ of the hemithorax.[5] Draining a pleural effusion secondary to pulmonary embolism is not necessary, but thoracentesis is sometimes done before the diagnosis is made or before anticoagulation is begun. If the patient is already anticoagulated, bleeding sites to which pressure cannot be directly applied should be minimized, precluding elective thoracentesis.

Low Cardiac Output

Clinical signs of low cardiac output after pulmonary embolism include tachycardia, weakness, and dyspnea with limited exertion. The reason is obstructed pulmonary arteries and an enlarged right ventricle encroaching on left ventricular filling. It is critical first to recognize that these signs point to serious cardiopulmonary compromise, whatever the oxygen saturation. Urine output should be monitored closely; oxygen and minimal exertion should be enforced, and the patient should be transferred to the intensive care unit and given pressor if required.[6]

Shock

Thrombolytic therapy should be considered if shock is due to pulmonary embolism and there is no contraindication. Drug choices include rt-PA (100 mg iv over 2 h), streptokinase (1.5 million units infused over 1 hour [an unapproved regimen][7]; or 250,000 units as a bolus, then 100,000 units/h for 24 h), and other drugs approved in various nations.[8] Other techniques, including pulmonary embolectomy, catheter clot fragmentation, pulmonary artery angioplasty, clot retrieval, and surgery on cardiopulmonary bypass have also been employed in selected patients.[9]

"Submassive Pulmonary Embolism"

Submassive pulmonary embolism is pulmonary embolism without shock but with echocardiographic evidence of right ventricular dysfunction. The argument for echocardiography in this setting is that echocardiography reveals many patients with right ventricular dysfunction (inconsistently defined) without overt shock, and that thrombolysis may save the lives of some such patients who would have a poor outcome. Thirty-one percent of acute pulmonary embolism patients have such findings without shock; this is 40% of the normotensive patients with pulmonary embolism.[10] Thrombolysis generally reduces pulmonary vascular obstruction when baseline and 24-h perfusion lung scans or pulmonary arteriography has been employed for evaluation. Moreover, a recently published controlled, partially blinded clinical trial[11] showed that if "escalation of therapy" were the outcome, rt-PA was superior to unfractionated heparin in such patients. The increased incidence of treatment escalation (25% in heparin versus 11% in t-PA recipients, $P = 0.006$) was due to a statistically significantly increased "requirement" for thrombolysis (determined after unblinding) in the heparin recipients (23% versus 8% in the t-PA recipients). Moreover, the heparin recipients had a higher incidence of major bleeding (3.6 versus 0.8%) and fatal bleeding, and no patients suffered hemorrhagic stroke. These safety results are quite contrary to prior reports. This study report prompted several rebuttal letters subsequently published.

The arguments against thrombolysis for submassive pulmonary embolism are that, although it improves pulmonary perfusion at the end of day 1, day 7 perfusion is not changed and mortality is not improved. Also, prior studies have shown it increases the intracranial hemorrhage rate from 0.2% with heparin alone to around 2.2%, and increases the major bleeding rate from around 2% with heparin alone to 6 to 15%, depending on the study.[12] Modeling of thrombolysis use employing the incidence figures cited above (not those from the recently published Konstantinides study) would lead to approximately 1800 excess hemorrhagic strokes per 300,000 incident patients with pulmonary embolism. This is a large safety cost, in addition to the economic cost. For these reasons, many experts recommend reserving thrombolysis for patients with shock.

Duration of Pulmonary Embolism Treatment

Most commonly, patients receive a minimum of 6 months of treatment. Occasionally, some physicians will use 3 months of treatment after relief of a temporary risk factor. The British Thoracic Society[13] recently

recommended 4 to 6 weeks of treatment in this latter circumstance, a recommendation with which the authors cannot agree. There is renewed interest in reimaging the pulmonary vasculature (eg, with a radionuclide perfusion scan or CT scan) when treatment cessation is considered, to confirm resolution or help decide, in conjunction with the patient, to continue therapy (see below, "Chronic Thromboembolic Pulmonary Hypertension").

Initial Anticoagulant Therapy

Initial anticoagulant therapy must be injected and continued for at least 5 days together with oral anticoagulant optimally started at the first day, and the patient must have an international normalized ratio (INR) >2.0 (target 2.5) for two consecutive days to assure it is safe to discontinue initial anticoagulant therapy.[8,14] Although sometimes this can be accomplished in 4 to 5 days, more often it takes 6 to 9 days in the setting of pulmonary embolism.[15] Since injected anticoagulants are more effective than oral anticoagulants, patients who are not recovering well from pulmonary embolism should remain on injected anticoagulant until they do substantially improve, even if the INR criterion is met earlier with an oral vitamin K antagonist. The latter patients can receive both drugs together.

There are several acceptable choices for initial anticoagulant therapy. They are unfractionated heparin, 80 U/kg iv bolus, and then 18 U/kg/h by continuous infusion in water with 5% dextrose. This should be regulated with frequent aPTT monitoring (eg, q 6 h) until it is 1.5 to 2.5 times the laboratory control value. Problems with this choice are (a) the requirement for frequent monitoring and dose adjustment; (b) the fact that evidence (Matisse investigators, unpublished data) suggests that if aPTT values fall below the target range, the risk of recurrence is increased; and (c) the requirement for laboratories to determine the therapeutic range with each new batch of aPTT reagents and equipment changes, a requirement not commonly met. Advantages of this choice are the short half-life of infused heparin (60 min) and reversibility with protamine sulfate (1 mg per 100 U unfractionated heparin) if bleeding ensues.

Fondaparinux given subcutaneous once daily (5 mg for <50 kg, 7.5 mg for 50 to 100 kg, 10 mg for >100 kg)[15] is approved in the USA for pulmonary embolism treatment. Its half-life is 16 h, allowing once-daily dosing. It does not require monitoring and was found comparable to iv heparin with respect to recurrence and bleeding in a large international clinical trial.[15] Advantages include minimal adjustment for weight, once daily dosing (self-administered or with a health provider daily check-up),

and the possibility of early discharge for selected patients at low risk for complications.

Several low molecular weight heparins have been studied for treatment in patients who have pulmonary embolism and concurrent deep vein thrombosis or deep vein thrombosis alone.[16-20] Although some are approved for once-daily dosing, twice-daily dosing is preferred by some experts to increase the chance of maintaining antithrombotic activity throughout a 24-h period (these drugs have considerably shorter half-lives than fondaparinux, eg, 6 h). Like fondaparinux, these do not require monitoring and selected patients may be discharged early after observation.[15,20]

Patients with significant renal insufficiency have impaired hemostasis and may require downward adjustment of low molecular weight heparin or fondaparinux dosage. Regardless of the anticoagulant received, if these patients bleed, hemostasis may require more attention than other patients.

Vena Cava Interruption

Recently developed retrievable inferior vena cava filters (and permanent ones) may be used when a contraindication to injected anticoagulant is sufficiently grave so as to prevent its use. When the contraindication remits, anticoagulant therapy should start. Implanted permanent vena cave filters significantly increase the rate of recurrent deep venous thrombosis at 2 years.[21]

Chronic Anticoagulation Therapy

Vitamin K antagonists (eg, warfarin, acenocoumarol, etc.) are begun orally, usually once daily, when patients are considered stable enough not to require immediate reversal of anticoagulation, because reversal with vitamin K and fresh frozen plasma requires many hours. These drugs are given in daily maintenance dosages rather than loading dosages (eg, 4 or 5 mg once daily of warfarin) and continued until the INR is >2.0 for two consecutive days. After the criterion of five consecutive days of injected anticoagulant therapy has been met, the injected anticoagulant can be discontinued if other criteria are met. In community practice, the INR target of 2.5 is rarely consistently achieved.[22] The range of 2.0 to 3.0 is met approximately 50% of the time. In specialty clinics and studies, it is met approximately two-thirds of the time, but clinicians should keep trying (see below).

Patients with Cancer

Patients with cancer have higher risks of recurrence and bleeding than other patients when given the above acute and chronic treatments. Several studies suggest that prolonged injected anticoagulant (low molecular weight heparin) provides a better result. In some centers, unless there is no way to pay for prolonged injected anticoagulant, cancer patients with pulmonary embolism receive prolonged low molecular weight heparin (eg, dalteparin 200 U/kg once daily for 1 month, then 150 to 160 U/kg once daily[23]; or enoxaparin[24]) for 5 months or longer. Some centers use different low molecular weight heparins with supportive but less compelling data.

Chronic Thromboembolic Pulmonary Hypertension

Recent data from the first published study[25] to follow the incidence of this disease in patients suffering a first pulmonary embolism demonstrated it occurred in 4% of patients and was established by 2 years after the first event. How to prevent this is uncertain at this time. Close attention to proper anticoagulation and sufficient oxygenation are reasonable suggestions while studies are developed. Patients with established thromboembolic pulmonary hypertension require therapeutic anticoagulation indefinitely, and possibly, thromboendarterectomy.

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The Role of Fibrinolytic Therapy in the Treatment of Venous Thromboembolism

Anthony J. Comerota, MD, FACS

Introduction

To appreciate the potential role of fibrinolytic therapy in the management of patients with venous thromboembolism, one needs to understand the long-term sequelae resulting from persistent obstruction of the pulmonary arteries due to pulmonary embolism (PE) and chronic obstruction and valvular dysfunction in lower extremity veins of patients having suffered deep venous thrombosis. Unfortunately, recently published guidelines addressing the management of patients with venous thromboembolism fail to endorse any treatment strategy designed to eliminate thrombus, in either the pulmonary arteries or the deep venous system of the lower extremities, unless the patient is at risk of dying or losing a limb.[1] Such recommendations under-serve our patients in light of available information. Within the space provided, current data will be reviewed and the rationale and results of fibrinolytic therapy for venous thromboembolism will be summarized.

Pulmonary Embolism

Chronic Thromboembolic Pulmonary Hypertension

The debilitating problem of chronic thromboembolic pulmonary hypertension following acute PE is greater than previously anticipated. In a recent prospective study of patients suffering their first episode of acute PE, Pengo and coworkers[2] demonstrated that within 2 years almost 4% of patients suffered chronic thromboembolic pulmonary hypertension. Risk factors associated with chronic thromboembolic pulmonary hypertension included younger age, a large perfusion defect, idiopathic pulmonary emboli, and previous pulmonary emboli. This important information suggests that acutely eliminating obstruc-

Dis Mon 2005;51:124-134
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.007

tion of the pulmonary vasculature might reduce chronic thromboembolic pulmonary hypertension.

National Institutes of Health Trials

The concept of improved cardiopulmonary function following lytic therapy for PE was substantiated by the National Institutes of Health (NIH) sponsored trials comparing urokinase and streptokinase to standard anticoagulation in patients with arteriographically documented PE.[3,4] These trials demonstrated that lytic therapy rapidly improved arteriographic and lung scan resolution of pulmonary emboli ($P < 0.05$) (Fig 1a-d). Patients receiving lytic therapy had significant improvement in their cardiopulmonary hemodynamics, with reduced pulmonary artery pressures and reduced right atrial pressures ($P < 0.05$), compared to patients treated with anticoagulation alone.

When these patients were studied at 1 year, those randomized to lytic therapy had greater pulmonary capillary blood volume and higher oxygen-diffusing capacity ($P < 0.05$) compared to patients treated with heparin.[5] This confirms that the basic functional unit of the lung was improved by acutely lysing the pulmonary embolus. The long-term functional benefit of lysis was further elucidated by Sharma and coworkers[6] when they performed right heart catheterizations in these patients 7 years following treatment. Patients treated with lytic therapy had lower pulmonary artery pressures and lower pulmonary vascular resistance ($P < 0.01$) compared to those treated with anticoagulation alone, and these differences were magnified with exercise. Patients treated with heparin had a nearly threefold increase in New York Heart Association (NYHA) functional class III-IV congestive heart failure compared to patients treated with thrombolysis (73% versus 25%).

A commonly presented argument is that lytic therapy has never been shown to reduce mortality of PE. This argument is invalid, since (1) a study was never designed to test the hypothesis of mortality reduction; (2) most patients randomized in the NIH-sponsored trials were not at risk for death; (3) a post-hoc analysis of patients at risk of death demonstrated mortality benefit from lysis; and (4) surrogate endpoints of cardiopulmonary morbidity and cardiopulmonary dysfunction demonstrate benefit from lysis.

Other Studies

A number of subsequent studies support the strategy of thrombolytic therapy for selected patients with PE. Goldhaber and coworkers[7] randomized 101 patients with acute PE to either rt-PA or heparin and

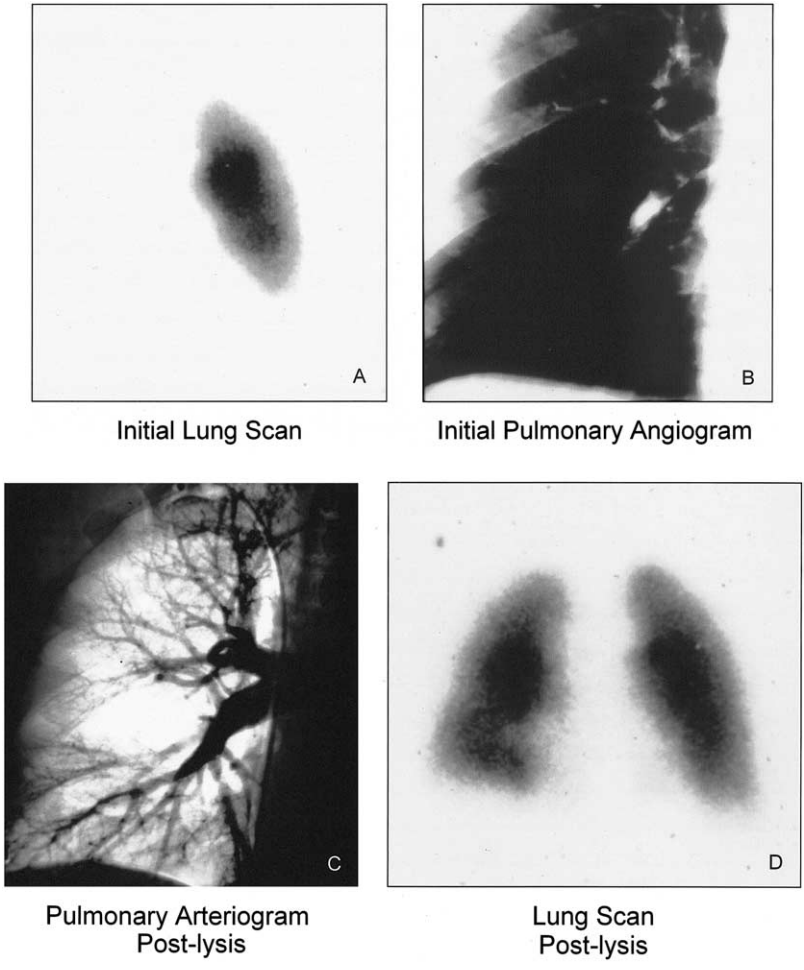

FIG 1. (a) Initial lung scan of a patient presenting with clinical signs and symptoms of PE. The scan showed no uptake of isotope in the right lung field. (b) Initial pulmonary arteriogram showing occlusion of the right main pulmonary artery associated with significant pulmonary hypertension. (c) Pulmonary arteriogram after 24 hours of thrombolysis. (d) Posttreatment perfusion scan showing reperfusion of the right lung field.

studied the outcome measures of right ventricular function and recurrent pulmonary emboli. Patients randomized to rt-PA had significantly improved right ventricular function at 24 hours ($P = 0.005$), a smaller end diastolic area of their right ventricle ($P = 0.01$), improved pulmonary perfusion ($P = 0.0001$), and reduced recurrent pulmonary emboli at 14 days ($P = 0.06$).

A multicenter international registry of thrombolytic therapy versus

anticoagulation reported a significantly lower 30-day mortality in patients receiving lytic therapy versus those receiving anticoagulation (4.7% versus 11.1%; $P = 0.016$).[8] Interestingly, primary lysis was the only independent predictor of survival on multivariate analysis. The only predictor of worse outcome in patients receiving lytic therapy was a history of recent surgery. All other characteristics, such as age, blood pressure upon presentation, the presence of syncope, and the status of the right ventricle, favored patients receiving lytic therapy. There was a greater incidence of major bleeding with lytic therapy; however, lytic patients had fewer recurrent pulmonary emboli.

Konstantinides and coworkers[9] conducted a randomized trial of submassive PE in 256 patients presenting with right ventricular dysfunction and pulmonary hypertension. Patients were randomized to heparin plus rt-PA versus heparin alone. The primary endpoint was a combination of in-hospital death and escalation of therapy, with secondary endpoints of recurrent pulmonary emboli and major bleeding.

There was a significant reduction in the combined primary endpoint in those patients treated with heparin plus rt-PA ($P = 0.006$). This was due predominantly to the need to escalate therapy and prevent ongoing clinical deterioration in patients randomized to anticoagulation. Interestingly, there were more bleeding complications in patients randomized to anticoagulation than in the rt-PA group.

Based upon the body of literature available for the management of patients with PE, it seems reasonable to adopt a strategy of lytic therapy in patients who present symptomatically with evidence of right ventricular dysfunction. Echocardiography should be part of the evaluation of all patients with PE. Those with evidence of right ventricular dysfunction, which includes enlargement of the right ventricle, right ventricular hypokinesis, increased pulmonary artery pressures, or tricuspid regurgitation, should be treated with a strategy to eliminate thrombus from their pulmonary vasculature (Fig 2).

Acute Deep Vein Thrombosis

The therapeutic goals for the management of patients with acute deep vein thrombosis (DVT) include (1) reduction of pulmonary emboli; (2) preventing extension of acute thrombosis; (3) reducing recurrence; (4) restoring patency to the occluded vein; (5) preserving venous valvular function; and (6) reducing the likelihood of chronic venous insufficiency. Unfortunately, anticoagulation alone does not restore patency, preserve valve function, or reduce the likelihood of chronic venous insufficiency,

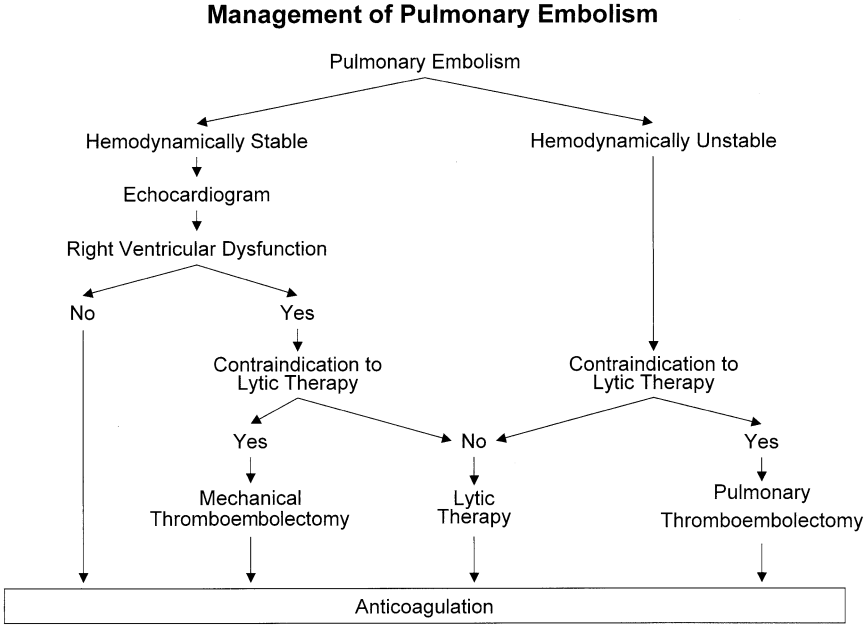

FIG 2. Algorithm for the management of patients with acute pulmonary embolism.

unless it is compared to no treatment. The therapeutic strategies, which include thrombus removal (thrombolytic therapy or venous thrombectomy), theoretically can achieve each of these therapeutic goals.

Evidence for the use of thrombolytic therapy for acute DVT derives from (1) an understanding of the pathophysiology of the postthrombotic syndrome; (2) experimental data; (3) natural history data of acute DVT (treated with anticoagulation); (4) a randomized trial of venous thrombectomy; and (5) data regarding catheter-directed thrombolysis, including the United States clinical experience, quality-of-life study, and a randomized trial.

The Epidemiology and Pathophysiology of the Postthrombotic Syndrome

The postthrombotic syndrome is due to the severe and often incapacitating sequelae of venous thrombosis, especially extensive DVT. When patients with iliofemoral DVT have been followed after being treated with anticoagulation alone, 15 to 40% develop the debilitating symptoms of venous claudication within 5 years,[10,11] 95% have documented venous insufficiency, and 15% will already have suffered venous ulceration.[10]

TABLE 1. Results of catheter-directed thrombolysis with urokinase in three contemporary series: efficacy and complications

Efficacy	Bjarnason et al[22] (*n* = 77)	Mewissen et al[23] (*n* = 287)	Comerota et al[24] (*n* = 58)
Initial success	79%	83%	84%
Iliac	63%	64%	78%
Femoral	40%	47%	—
Primary patency at 1 year			
Iliac	63%	64%	78%
Femoral	40%	47%	—
Iliac Stent: Patency at 1 year			
+Stent	54%	74%	89%
−Stent	75%	53%	71%
Complications			
Major bleed	5%	11%	9%
Intracranial bleeding	0%	<1%	0%
Pulmonary embolism	1%	1%	0%
Fatal pulmonary embolism	0%	0.2%	0%
Death secondary to lysis	0%	0.4%	0% (? 2%)*

*Death due to multiorgan system failure 30 days postlysis, thought not related to lytic therapy.

The underlying pathophysiology of the postthrombotic syndrome is ambulatory venous hypertension.[12] This is defined hemodynamically by elevated venous pressures with exercise.[12,13] The components of ambulatory venous hypertension include vein lumen obstruction and valvular incompetence. The combination of obstruction and incompetence are associated with the highest ambulatory venous pressure and the most severe form of postthrombotic syndrome.[13,14] It appears intuitive that if obstruction can be eliminated, the underlying pathophysiology will be substantially reduced. If valvular function is maintained, the pathophysiology of the postthrombotic syndrome will be eliminated and the clinical sequelae will be avoided.

Experimental Data

Cho and coworkers[15] and Rhodes and coworkers[16] in a canine model of acute DVT demonstrated that thrombolysis with urokinase was potentially beneficial. They studied vein valve function and endothelial function. Following treatment with urokinase, vein valve function and endothelial-dependent relaxation was preserved acutely and at 4 weeks following thrombolysis. In the thrombolysis-treated animals, there was less residual thrombus and structural and functional venous integrity was maintained.

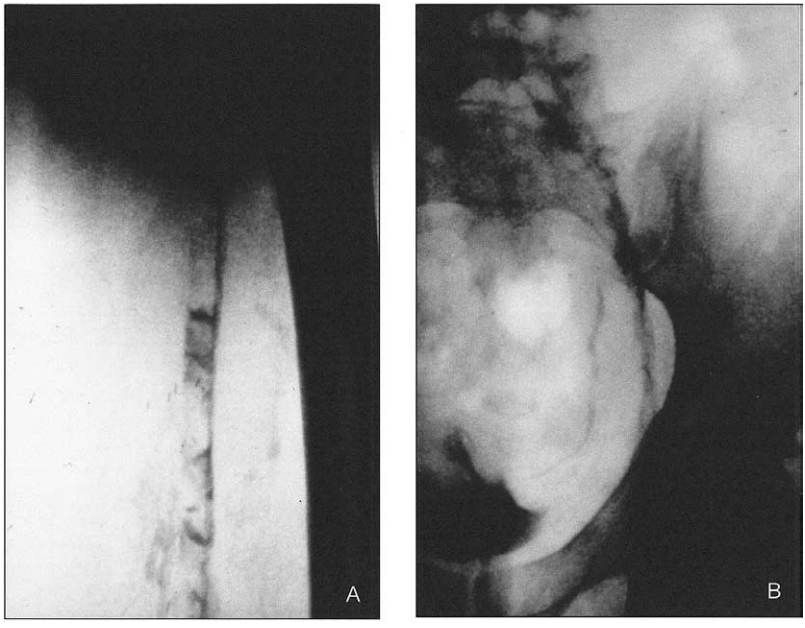

FIG 3. The initial ascending phlebogram of a patient with acute iliofemoral DVT demonstrates acute thrombus in the femoral vein (A) and the iliac veins (B). Following intrathrombus catheter-directed thrombolysis via an ultrasound-guided popliteal vein approach, patency is restored to the femoral vein (C) and the iliofemoral venous system (D). However, lysis revealed an underlying left common iliac vein stenosis. The stenosis is improved following balloon angioplasty, but it is not corrected (E). Following stenting of the left common iliac vein, unobstructed venous drainage into the vena cava is achieved (F). The patient was therapeutically anticoagulated with a warfarin compound and remains asymptomatic.

Natural History of Acute DVT Treated with Anticoagulation

In a large natural history trial, Markel and coworkers[17] demonstrated that persistent obstruction of proximal veins was associated with distal valve incompetence. Johnson and coworkers[14] and Shull and coworkers[13] showed that the combination of venous obstruction and venous valvular incompetence was associated with the highest ambulatory venous pressures and the most severe postthrombotic morbidity. Meissner and coworkers[18] demonstrated that some patients went on to spontaneously lyse their thrombus. Those who lysed their thrombus within 60 days of treatment had restored patency and a significantly higher likelihood of preserving venous valvular function.

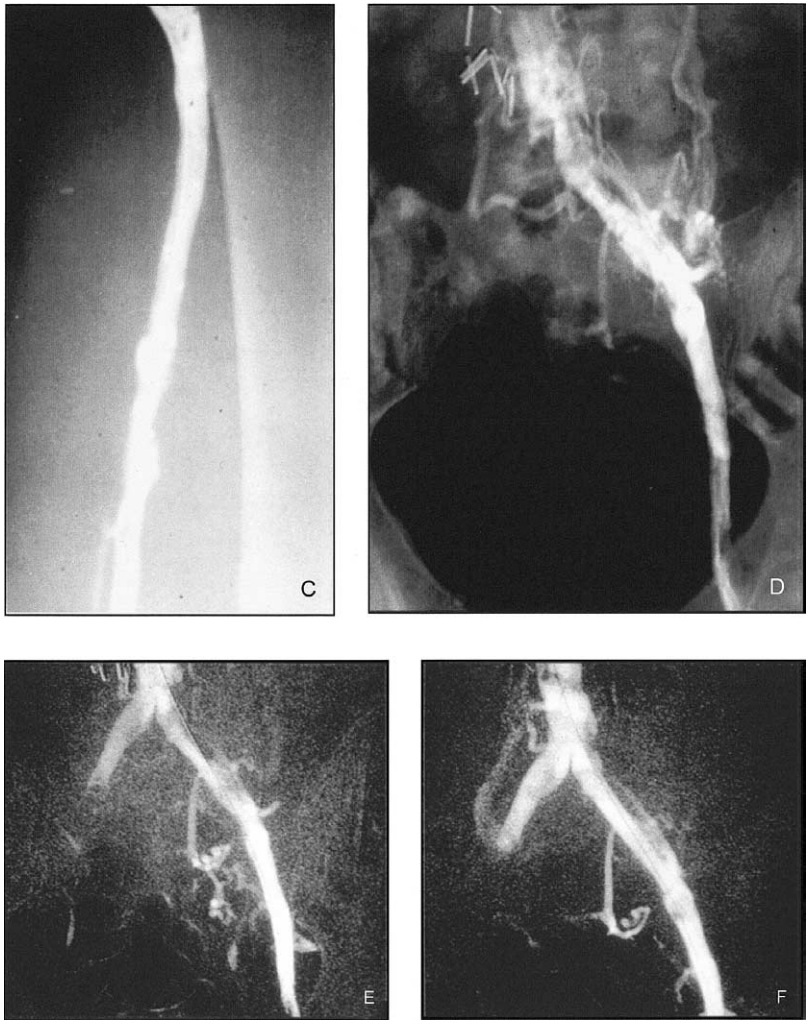

FIG 3. Continued

Venous Thrombectomy Versus Anticoagulation

A large multicenter randomized trial evaluating venous thrombectomy plus anticoagulation versus anticoagulation alone in patients with iliofemoral DVT was performed by the Scandinavian investigators. Patients were objectively evaluated at 6 months,[19] 5 years,[20] and 10 years.[21] Endpoints assessing venous patency, venous pressures, leg swelling, and symptoms of the postthrombotic syndrome all resulted in better outcomes in patients who were operated compared to those treated with anticoagulation alone.

These data from a randomized trial suggest that thrombus removal plus anticoagulation is significantly better than anticoagulation alone for patients with extensive DVT.

Catheter-Directed Thrombolysis

Many clinicians have observed significant clinical improvement defined by a marked reduction or elimination of the postthrombotic syndrome in patients having iliofemoral DVT treated with catheter-directed thrombolysis.[22-25] Elsharawy and coworkers[26] confirmed these observations when they randomized 35 patients with iliofemoral DVT to anticoagulation ($N = 17$) or catheter-directed thrombolysis plus anticoagulation ($N = 18$). At 6-month follow-up the patients treated with catheter-directed lysis had significantly better patency and valve function compared to those treated with anticoagulation.

Large contemporary series from the United States have demonstrated consistent results suggesting that success could be achieved in the majority of patients[22-24] (Table 1). The principles of catheter-directed thrombolysis incorporate intrathrombus infusion of a lytic agent and correcting any underlying venous lesion to provide unobstructed venous drainage into the vena cava (Fig 3a-f). Achieving this, one can expect 95% patency at 1 year with excellent clinical outcomes.[23] Catheter-directed thrombolysis for iliofemoral DVT has been associated with a significantly improved quality of life at 16 and 22 months following treatment compared with anticoagulation alone[27] (Table 2). Lytic patients had better physical functioning, less health distress, less stigma of chronic venous disease, and fewer postthrombotic symptoms. Not surprisingly, successful catheter-directed thrombolysis directly correlated with improvement of quality of life.[27] Those patients who had failure of lytic therapy had similar quality of life as those treated with anticoagulation alone.

On the basis of the large volume of available information, it is reasonable to offer patients with severely symptomatic DVT and those with iliofemoral DVT the option of catheter-directed thrombolysis. An understanding of the pathophysiology of the postthrombotic syndrome, experimental data, a large volume of observational data in case-controlled studies, and a randomized trial suggest that catheter-directed thrombolysis will reduce the postthrombotic syndrome, thereby improving outcome.

A larger, more robust trial is needed to definitively prove catheter-directed thrombolysis as the preferred initial treatment. Until then, knowledgeable practitioners should endorse a strategy of thrombus removal with catheter-directed thrombolysis for patients who are physi-

TABLE 2. Quality-of-life outcome at 16 months following treatment of iliofemoral DVT: successful lysis versus anticoagulation[27]

	Successful Lysis (n = 43)	Anticoagulation (n = 30)	*P* Value
Health utilities index	0.83	0.74	0.032
Role functioning physical	75.68	58.59	0.013
Treatment satisfaction	86.59	81.72	0.490
Stigma	85.98	71.32	0.033
Health distress	82.48	64.11	0.007
Overall symptoms	78.55	55.56	<0.001

cally active and at low risk for lytic therapy, and contemporary venous thrombectomy for patients at high risk for thrombolysis.

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Immediate Ambulation and Leg Compression in the Treatment of Deep Vein Thrombosis

Hugo Partsch, MD

Introduction

The introduction of subcutaneous injections of low molecular weight heparin (LMWH) instead of intravenous infusions with unfractionated heparin (UFH) allowed one to recommend home treatment of patients with deep-vein thrombosis (DVT).[1]

However, the practically important question of when and how intensively these patients can ambulate is not addressed in DVT studies and meta-analyses advocating home therapy, nor in most recommendations and patients' brochures.[2-4] Until recently it was also not clear if adjuvant compression therapy is of any beneficial value in the acute stage of DVT.

Why Bed Rest in Acute DVT?

The fear of dislodged clots causing serious or fatal pulmonary embolism (PE) has been the reason for the traditional recommendation of bed rest for some days in combination with anticoagulation. The belief that pain and swelling would be improved faster by immobilization was an additional argument favoring bed rest. Only a few studies question these dogmas.

Bed Rest Does Not Prevent PE

A retrospective multicenter study of 1647 patients with DVT treated conservatively by UFH and bed rest in different German hospitals reported a rate of fatal PE of 2.33%.[5] Between 1993 and 2000 we treated 1289 consecutive, mobile patients with acute DVT with LMWH, compression, and immediate ambulation in the hospital. One hundred ninety-five patients with iliofemoral thrombosis underwent MRI that demonstrated clots in the inferior caval vein in 41 cases (21%). V/Q scans were performed at admission and repeated after 10 days.[6] PE was demonstrated in the baseline scan in 190/356 (53.4%) of iliofemoral, 355/675 (52.6%)

Dis Mon 2005;51:135-140
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.008

of femoral, and 84/239 (35.1%) of lower leg vein thrombosis (difference iliofemoral and femoral versus lower leg DVT, $P < 0.001$). Two-thirds of these PE had no clinical lung symptoms. In comparison to the baseline scan, new PEs occurred in 7.4, 6.4, and 3.4%, respectively, after 10 days. Only 6/77 patients with scintigraphically detected new PEs had mild pulmonary symptoms. Seventeen of the 1289 (1.32%) patients died and all underwent autopsy. Only three deaths (0.23%; 95% CI 0.048 to 0.678) were caused by PE, all patients being older than 76 years. The most frequent cause of death in the 17 patients was malignancy.

Our study shows that about half of patients with proximal DVT who come in walking have pulmonary emboli detected by lung scan, but most of these emboli are asymptomatic. When these patients are treated with adequate doses of LMWH and kept walking with good compression, the life-threatening danger is over. New PEs occur very rarely, and if they do, are mostly asymptomatic. We have observed fatal PE with a frequency of 3/1289 (0.2%) in the elderly and in patients with additional severe diseases.

Two randomized controlled trials have proven that there was no statistically significant difference in the frequency of new PEs compared to a baseline scan if patients with proximal DVT treated with LMWH were kept in bed or walked around with leg compression. The authors of both studies conclude that bed rest as an additional measure in the treatment of DVT is not able to substantially reduce the incidence of scintigraphically detectable pulmonary embolism and that early mobilization is safe.[7,8]

A recent systematic review from Spain also demonstrates that early mobilization does not increase the rate of PE or the complication rate.[9]

Bed Rest Promotes Stasis and Thrombus Propagation

Bed rest promotes venous stasis and obviously has more risks concerning thrombus propagation and other complications, especially in older patients. In a retrospective analysis of phlebographic studies comparing thrombus extension in the initial stage with the result several days later, thrombus propagation was demonstrated in 26% if patients were kept at bed rest for more than 5 days, but only in 1% if mobilization was started between day 0 and 2.[10] Most of the studies in which patients with DVT had bed rest and were treated by UFH given intravenously demonstrate similar results, with thrombus progression in about 20 to 30% despite exact anticoagulation.[11]

Immediate Mobilization Reduces Thrombus Growth

In a randomized controlled trial in a total of 53 patients with proximal DVT, bed rest without compression was compared with walking exercises using either compression stockings or bandages. All patients were treated with LMWH and the thrombus size was assessed by Duplex examination on day 0 and day 9. A progression of thrombus length in the femoral vein was seen in 40% after bed rest and in 28% with walking and compression (NS). Taking into account the change of thrombus length, the difference between bed rest and walking with compression was statistically significant ($P < 0.01$).[12]

The influence of mobilization on thrombogenesis is not well investigated. In a recently published experiment it was demonstrated that exercise suppresses shear-induced platelet activation and subsequent polymorphonuclear leukocyte adhesion to platelets deposited at sites of vascular injury under flow and thereby reduces the risk of vascular thrombosis and inflammation.[13]

Compression and Walking Reduce Pain and Swelling More than Bed Rest

In the above-mentioned randomized controlled trial on 53 patients with proximal DVT, all treated by dalteparin, 200 IU/kg per body weight, 18 patients received strong Unna boot bandages; 18 patients received thigh-length compression stockings class II, and 17 patients underwent bed rest without compression. In the mobile compression groups the walking distance measured by a pedometer was between 600 and 12,000 m per day. Pain level was assessed by visual analog scale and by comparing the pain level between both legs when a blood pressure cuff producing a steadily increasing pressure to the calf was applied (modified Lowenberg test). The Lowenberg test reflects a more objective parameter for pain and allows a fair comparison between walking and bed-rest patients who would not experience pain as long as they do not walk. This test revealed a constantly elevated pain level in the bed-rest group after 3 days of initial improvement, in contrast to the walking groups with compression, who showed a continuous improvement. The completely inelastic zinc plaster bandages with a pressure on the distal lower leg of about 50 mm Hg gave better results than elastic stockings exerting a pressure of 35 mm Hg. After 9 days the pain level and the difference between the circumferences of both calves were significantly more reduced in the compression groups compared with the bed-rest group ($P < 0.01$). Nearly all mobilized patients were free of pain and edema. There

was no significant difference concerning the occurrence of new pulmonary emboli assessed by repeat V/Q scan.[12,14]

Pain and swelling of the leg with symptomatic DVT have considerable subjective relevance for the patient. Up to now these clinical signs and symptoms have been widely neglected in most studies concentrating on therapeutic outcome.

Immediate Mobilization and Compression May Prevent Postthrombotic Syndrome

In some centers the patient with DVT is advised to stay in bed with elevated legs for the first few days to reduce pain and swelling and only then to start with mobilization. Hull and coworkers have demonstrated that an inadequate quality of initial anticoagulant response to heparin in the first 24 hours increases the recurrence rate in the next 3 months.[15] Putting a patient into bed for 24 hours will certainly also promote thrombus propagation during this time. Therefore, after diagnosis of DVT is made and LMWH is initiated, patients who were not immobilized up to this moment should be encouraged to ambulate immediately, which is tolerated very well by most patients if leg compression is strong enough.

Two randomized controlled trials have compared the late outcome several years after acute, symptomatic proximal DVT in patients who wore compression stockings with those who did not.[16,17] Both studies, one performed with custom-made thigh-length stockings and one using calf-length, ready-made stockings, showed that consequent wearing of compression stockings could reduce the frequency of a postthrombotic syndrome to one-half. To date there are no convincing data available that similar effects can be achieved with long-term anticoagulation.[11] In both studies, compression therapy was started only after discharge from the hospital and not immediately after the diagnosis of DVT was made. Therefore, we have followed our patients in the above-mentioned randomized controlled trial for an average period of 2 years. Judged by the Prandoni scale, which combines five subjective symptoms with six objective signs,[18] a significantly better outcome could be found in the mobile group (median score 5.0) than in the bed-rest group (median score 8.0) ($P < 0.01$) ("Mild PTS"= score 5 to 14, "severe PTS" score $\geq$15).[19]

Mobile Patients with DVT Should Be Encouraged to Walk with Firm Compression

The idea to apply firm bandages and to keep patients with deep vein thrombosis mobile was been advocated in 1910 by Heinrich Fischer, a

pupil of Unna, who recommended firm zinc plaster bandages (Unna boots) and walking exercises to treat patients with DVT.[20] It took a long time before the following recommendation in the recent ACCP Consensus document was formulated: "For patients with DVT, we recommend ambulation as tolerated (Grade 1B)."[21]

Conclusion

In general, bed rest is a potentially harmful treatment needing more careful evaluation.[22] This is also true for symptomatic, mobile outpatients with DVT, especially for those in higher age groups. At least for those patients for whom thrombolytic or surgical therapy is not indicated or feasible, we recommend starting treatment with therapeutic doses of LMWH and keeping mobile patients ambulant, encouraging them to walk as much as possible with good compression. For those therapists who are not able to apply a strong and well-fitting multilayer short-stretch bandage, good-quality compression stockings, class II to III, may be an alternative. Compression should be recommended for 2 years, depending on signs and symptoms. We need more studies in which the optimal dosage of the important antistasis measures of compression and walking should be evaluated.

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Heparin-Induced Thrombocytopenia

Theodore E. Warkentin, MD, FRCP(C), FACP

Introduction

A discussion of venous thromboembolism (VTE) is incomplete without considering the topic of heparin-induced thrombocytopenia (HIT), for three reasons. First, VTE is almost always initially treated with heparin, thus creating the potential for the patient to develop this immune-mediated adverse effect. Second, VTE itself is the most common complication of HIT. Third, the treatment of deep-vein thrombosis (DVT) in HIT with warfarin poses the risk of precipitating severe venous limb ischemia, with the potential for limb loss (venous limb gangrene).

Definition

HIT can be defined as any clinical event best explained by platelet factor 4 (PF4)/heparin-reactive antibodies ("HIT antibodies") in a patient who is receiving, or who has recently received, heparin.[1] In the majority of patients, this includes a large platelet count fall that usually exceeds 50%. The clinical importance of HIT primarily stems from its bizarre association with thrombosis, which occurs in 35 to 70% of patients. Table 1 lists four risk factors for HIT.[2-6]

Pathogenesis

HIT is caused by platelet-activating antibodies of IgG class that recognize a "self" protein, PF4, bound to heparin.[7] Multimolecular complexes of PF4, heparin, and IgG form on platelet surfaces, leading to platelet activation via occupancy of the platelet Fcγ receptors. Heparin molecules bind to PF4 in relation to their chain length, perhaps explaining why unfractionated heparin is more likely to cause HIT than low-molecular-weight heparin.[2-5] Platelet activation in HIT is also accompanied by profound activation of coagulation. Once triggered, the prothrombotic risk of HIT remains for several days to a few weeks, even after stopping heparin.[8,9]

Dis Mon 2005;51:141-149
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.009

TABLE 1. Risk factors for HIT

Risk Factor	Relative Risk (Estimate)
Unfractionated > low-molecular-weight heparin[2-5]	10-40
Duration of heparin (10-14 vs <4 days)[3-5]	5-10
Postoperative (surgical) > medical/pregnant patient[5]	3-5
Gender (female > male)[6]	1.5-2

TABLE 2. Estimating the pretest probability of HIT: the "four T's"

	Points (0, 1, or 2 for each of four categories: maximum possible score = 8)		
	2	**1**	**0**
Thrombocytopenia	>50% platelet fall to nadir ≥20	30–50% platelet fall, or nadir 10-19	<30% platelet fall, or nadir <10
Timing* of onset of platelet fall (or other sequelae of HIT)	Days 5-10, or ≤day 1 with recent heparin (past 30 days)	>Day 10 or timing unclear; or <day 1 with recent heparin (past 31-100 days)	<Day 4 (no recent heparin)
Thrombosis or other sequelae	Proven new thrombosis; skin necrosis; or acute systemic reaction after i.v. heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven)	None
O**T**her cause(s) of platelet fall	None evident	Possible	Definite

Pretest probability score: 6-8 = High; 4-5 = Intermediate; 0-3 = Low

Modified from ref [11], with permission.
i.v., intravenous.
*First day of immunizing heparin exposure considered day 0.

Clinical Presentation

Thrombocytopenia is common in heparin-treated patients, and only a minority have HIT. A clinical scoring system, the *Four T's*, is useful in predicting which thrombocytopenic patients have HIT, based upon assessment of ***T***hrombocytopenia, ***T***iming, ***T***hrombosis, and the absence of o***T***her explanation(s) for thrombocytopenia (Table 2).[1,10,11] Preliminary evaluation suggests that HIT antibodies are unlikely (<5%) when a low score (≤3) is obtained, but very likely (>80%) with a high score (≥6).[12] An intermediate score (4 or 5) indicates a clinical profile compatible with HIT but also with another plausible explanation, such as sepsis; laboratory testing for HIT antibodies is especially valuable in these patients.

TABLE 3. Thrombotic and other sequelae of HIT

VENOUS: lower-limb deep-vein thrombosis (50%); pulmonary embolism (25%); upper limb deep-vein thrombosis (10% with central venous catheters); adrenal hemorrhagic necrosis (3%; if bilateral, acute adrenal crisis results); other (<3%, eg, cerebral venous [dural sinus] thrombosis, mesenteric vein thrombosis)
ARTERIAL: limb artery thrombosis (5-10%), thrombotic stroke (3-5%), myocardial infarction (3-5%), other (<3%, eg, mesenteric artery thrombosis, distal aortic thrombosis, spinal artery thrombosis, renal artery thrombosis)
MICROVASCULAR: coumarin-induced venous limb gangrene or skin necrosis (5-10% of patients treated with coumarin); acral limb ischemia or livedo reticularis secondary to decompensated DIC (<3%)
SKIN LESIONS at heparin injection sites: either erythematous plaques or skin necrosis (5-10% of HIT patients receiving subcutaneous heparin injections)
ACUTE SYSTEMIC REACTIONS after intravenous heparin bolus: one or more of the following symptoms or signs: inflammatory (fever, chills, flushing), cardiorespiratory (tachycardia, hypertension, tachypnea, dyspnea, chest pain), neurologic (pounding headache, transient global amnesia), or gastrointestinal (diarrhea) (25% of HIT patients receiving an intravenous heparin bolus)

Most patients with HIT have mild or moderate thrombocytopenia, with platelet count nadirs between 20 and 150 $\times$ 10^9/L (median nadir, 55 $\times$ 10^9/L); only 5 to 10% develop a platelet count fall to less than 20 $\times$ 10^9/L.[1] At least 90% evince a 50% or greater platelet count fall; especially in postoperative patients (who usually exhibit thrombocytosis beginning after postoperative day 5), the platelet count nadir does not necessarily fall below 150 $\times$ 10^9/L.[4] Typically, the platelet count begins to fall 5 to 10 days after starting heparin, although a rapid platelet count fall (within 24 hours) can occur if HIT antibodies are already present because of recent exposure to heparin.[13] This link between "rapid-onset HIT" and *recent* heparin exposure is explained by the remarkable transience of HIT antibodies, which become undetectable at a median of 50 to 80 days (depending on the assay performed) after an episode of HIT.[13] Indeed, the transience of HIT antibodies, together with the inability to regenerate HIT antibodies before day 5 following re-exposure, provides a rationale for using heparin anticoagulation during cardiac surgery in a patient with previous HIT, provided that HIT antibodies are no longer detectable when surgery is performed.[14,15] Rarely, HIT begins several days after heparin has already been stopped (*delayed-onset HIT*); this syndrome is associated with strongly positive tests for HIT antibodies, including the ability of the patient's serum to activate platelets in vitro without the need to add heparin.[16]

Thrombosis is the most important complication of HIT and occurs in the majority of patients (Table 3).[1,3-5,8,9,10] The odds ratio for thrombosis ranges from 20 to 40.[15]

Venous Thrombosis and HIT

Venous thrombosis is the most common thrombotic complication of HIT[1,3-5,8-10]: DVT occurs in about 50% of patients, with half of these suffering from symptomatic pulmonary embolism.[1,8,10] Venous limb ischemia (phlegmasia cerulea dolens, venous limb gangrene) can result if coumarins such as warfarin are used to treat DVT associated with HIT.[10,17] This arises from a profound disturbance in procoagulant–anticoagulant balance: HIT creates hypercoagulability (increased thrombin generation) and coumarin leads to severe depletion of the vitamin K dependent natural anticoagulant, protein C. A *supra*therapeutic international normalized ratio (INR usually >4.0) is characteristic of venous limb ischemia and represents a surrogate marker for severe protein C depletion (via parallel reduction in factor VII).[10] Rarely, overt (decompensated) disseminated intravascular coagulation can explain microvascular thrombosis and limb ischemia in the absence of coumarin treatment.[10] Venous limb gangrene is a more common explanation for limb loss than the classic "white clot syndrome" of HIT whereby large limb arteries are occluded by pale, platelet-rich thrombi.[10,17]

Laboratory Testing for HIT Antibodies

Two types of assays detect HIT antibodies.[1,11] Most widely used are the commercial enzyme-immunoassays (EIAs) that test for antibodies reactive against PF4/heparin or PF4/polyvinyl sulfonate.[18] In contrast, platelet activation assays exploit the platelet-activating property of pathogenic HIT antibodies. The best platelet activation assays utilize "washed" platelets, eg, the platelet serotonin release assay. However, this test is technically demanding, available in only a few reference laboratories, and requires careful quality control for optimal results.[19]

Iceberg Model

Figure 1 shows the relationship between these HIT antibody assays, thrombocytopenia (clinical HIT), and HIT-associated thrombosis.[3-5] The following four features are illustrated: (1) both washed platelet activation assays and EIAs have similar high sensitivity for clinical HIT; (2) the washed platelet activation assays have higher diagnostic *specificity* for clinical HIT than the EIAs (although noncommercial "in-house" EIAs that only detect HIT-IgG antibodies are superior to commercial EIAs,[20] which also detect nonpathogenic IgM and IgA class antibodies); (3) only a subset of heparin-treated patients who form platelet-activating PF4-reactive IgG develop clinical HIT; and (4) increased risk of thrombosis is

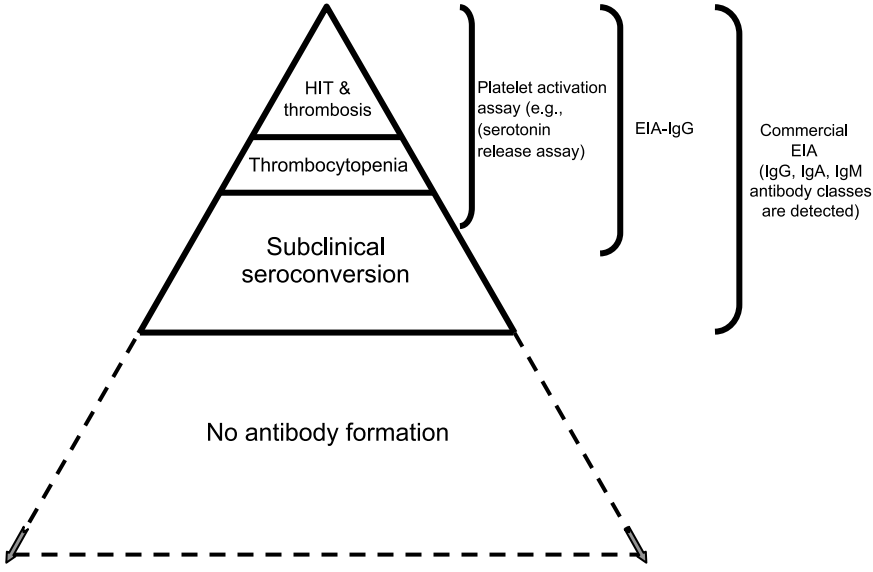

FIG 1. Iceberg model of HIT. Although "antigen" assays, such as the commercial enzyme immunoassays (EIAs), which detect antibodies of IgG, IgM, and IgA classes, are more sensitive than platelet activation assays for detecting PF4/heparin-reactive antibodies, many nonpathogenic antibodies are also detected by the EIAs. Thus, the platelet activation assays (eg, platelet serotonin release assay using "washed" platelets) are not only equally sensitive for clinical HIT than the EIAs, they also have much greater diagnostic specificity. EIAs that detect only PF4/heparin-reactive antibodies of IgG class (not commercially available) have high sensitivity and intermediate diagnostic specificity.

not observed in patients who develop antibodies in the absence of a significant platelet count fall.

Treatment

In patients strongly suspected of having HIT, the physician should discontinue all heparin and institute an appropriate nonheparin anticoagulant. This recommendation applies even to patients without clinically evident thrombosis when HIT is diagnosed, given the unfavorable natural history of "isolated HIT" (25 to 50% risk of symptomatic thrombosis, including 5% thrombotic death rate).[1,8,9,14] In the U.S., two *direct thrombin inhibitors* (DTIs) are approved for treating thrombosis complicating HIT.[14,15] In some jurisdictions (though not the U.S.), danaparoid (mixture of nonheparin anticoagulant glycosaminoglycans) is approved and available. Other marketed anticoagulants with favorable (albeit minimal) "off-label" experience in HIT include bivalirudin and fondaparinux.[14]

Warfarin is ineffective in acute HIT and predisposes to microvascular thrombosis. Venous limb gangrene (acral necrosis) is a more common manifestation of "coumarin necrosis" in HIT patients than is classic skin necrosis.[17,21] It is recommended[14] that warfarin be delayed in HIT until substantial resolution of thrombocytopenia has occurred (preferably, platelet count greater than 150×10^9/L), with subsequent cautious DTI–warfarin overlap (eg, avoid warfarin loading doses; provide minimum 5-day overlap; discontinue DTI when platelet count has normalized and reached a steady plateau).[14] Administration of vitamin K is advised when HIT is diagnosed only after warfarin has already been started[14]: besides reducing risk of coumarin necrosis, this might avoid DTI underdosing (since warfarin prolongs the activated partial thromboplastin time [APTT] used to monitor the DTI).

Prophylactic platelet transfusions are not recommended, as petechiae and other evidence of impaired hemostasis is not usually seen in HIT, and transfused platelets might contribute to increased thrombotic risk. In my opinion, vena caval filters should be avoided, as their use in acute HIT seems to be complicated frequently by massive lower limb venous thrombosis.

Given the high frequency of clinical and subclinical DVT, routine duplex ultrasonography is recommended.[14] Testing for HIT antibodies provides important corroborative (if strongly positive) or contrary (if negative or only weakly positive) information. Particularly if an alternative explanation for thrombocytopenia becomes apparent, a negative test for HIT antibodies allows the possibility of resuming heparin treatment.

Lepirudin

Lepirudin is a recombinant hirudin that forms irreversible 1:1 complexes with thrombin.[22,23] Its half-life (about 80 min) increases dramatically in renal insufficiency. As no antidote exists, major dose reduction (or avoidance) is required for patients with renal compromise. The approved dose (normal kidneys) is 0.4 mg/kg by intravenous bolus followed by an initial infusion rate at 0.15 mg/kg/h, adjusted for target APTT 1.5 to 2.5 times baseline. However, in the absence of severe thrombosis, and to reduce bleeding risk, some experts advise omitting the initial bolus, using a lower target APTT (1.5 to 2.0 times baseline), and monitoring the APTT every 4 hours until steady state is established.[22-24]

Compared with historical controls, lepirudin was associated with reduced thrombotic events (relative risk reduction [RRR], 0.63 to 0.78).[14,15,25] Lepirudin also was effective for patients with isolated

HIT using a lower dose protocol (0.10 mg/kg/h adjusted by APTT without initial bolus).[24]

Lepirudin is a foreign (leech-derived) protein, and its use can trigger antihirudin antibodies that can alter pharmacokinetics, including drug accumulation from impaired renal excretion of lepirudin–IgG complexes. Fatal anaphylaxis following intravenous bolus administration has been reported.[26]

Argatroban

Argatroban is approved to treat both HIT complicated by thrombosis and isolated HIT.[27,28] It is a small-molecule DTI that (unlike lepirudin) is not immunogenic. The usual dose is 2 μg/kg/min adjusted by APTT (usual target, 1.5 to 3 times baseline APTT). Compared with historical controls, argatroban was associated with reduced thrombotic events (RRR, 0.44 to 0.62).[14,15,27,28] The starting dose should be reduced by 75% in a patient with significant liver dysfunction, since argatroban undergoes hepatobiliary excretion. Prolongation of the INR by argatroban is considerably greater than with lepirudin,[22] which can complicate argatroban–warfarin overlap; this underscores the importance of postponing warfarin pending substantial resolution of HIT.

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Deep Vein Thrombosis and Cancer: Survival, Recurrence, and Anticoagulant Choices

Agnes Y. Y. Lee, MD, MSc, FRCP(C)

Introduction

Approximately one-quarter of all cases of venous thromboembolism (VTE) are related to underlying malignancy. In patients with newly diagnosed VTE, about 20% already have cancer, while in patients with idiopathic VTE, about 10% are diagnosed with malignancy within the next 12 months.[1,2] Consequently, many physicians are faced with the challenging task of managing VTE in cancer patients, in whom the risks of recurrent thrombosis and serious bleeding are high. Furthermore, given that the life expectancy of cancer patients with VTE is significantly shorter than similar cancer patients without this complication,[3,4] quality of life is a particularly important consideration when treating these patients. The reasons for the higher mortality rate in cancer patients with VTE are unknown, but possible explanations include premature death from fatal pulmonary embolism (PE); VTE being a paraneoplastic marker of aggressive malignancies; or activation of coagulation promoting tumor growth.[5-7] Evidence is now emerging that low-molecular-weight heparins (LMWHs) may be able to interrupt this latter process and improve patient survival.[8-11]

Initial Therapy of VTE

Low-Molecular-Weight Heparin or Unfractionated Heparin

The standard anticoagulants for the initial treatment of acute VTE are unfractionated heparin (UFH) and LMWH. According to the most recent meta-analysis of the randomized trials comparing these agents, LMWH is more effective and safer than UFH.[12] Furthermore, LMWHs can be given in an outpatient setting without the need for laboratory monitoring and have a lower risk of heparin-induced thrombocytopenia.[13] In many

Dis Mon 2005;51:150-157
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.010

developed countries, outpatient LMWH has become the standard of care for the initial treatment in patients with DVT or hemodynamically stable PE.

Whether LMWHs and UFH are equally effective and safe in patients with cancer has not been formally investigated. Based on published data extracted from trials that reported on the outcomes of the subgroup of cancer patients, it appears that LMWHs and UFH have similar efficacy in patients with and without cancer (Table 1).[14-17] Data on the bleeding risk of therapeutic doses of LMWH compared with UFH in cancer patients have not been published. Clearly, outpatient LMWH therapy reduces hospitalization and cohort studies have shown that cancer patients can be treated safely at home with LMWH.[18-21]

Once or Twice Daily Dosing of Low-Molecular-Weight Heparin

Subcutaneous LMWH may be administered either once daily or twice daily and some agents have regulatory approval for both regimens. Significant differences in efficacy and safety between these regimens have been shown, although some studies have suggested that twice-daily injection may be more efficacious.[17,22] Given the hypercoagulable status of cancer patients, it is possible that twice-daily administration of a LMWH is required to provide a more steady state of anticoagulation, but this hypothesis has not been properly tested. Until further evidence is available, once-daily injection is the acceptable practice.

Long-Term Therapy

Vitamin K Antagonists

Vitamin K antagonists are the mainstay of long-term anticoagulant treatment for preventing recurrent VTE and warfarin is the most commonly used agent.[13] Warfarin is started within the first 24 hours of diagnosis and is continued for a minimum of 3 months. Due to differences

TABLE 1. The efficacy of LMWH and unfractionated heparin for initial therapy of VTE in patients with and without cancer

	3-Month Incidence of Symptomatic Recurrent VTE			
	No. of Patients	**LMWH (%)**	**UFH (%)**	***P* Value**
Cancer	546	9.2	9.2	NS
No cancer	2275	4.0	4.2	NS

Combined results from four randomized trials showing the 3-month rates of recurrent VTE separately for patients with and without cancer.[14-17]

in the anticoagulant response between patients and within patients over time, dose adjustments are needed based on the international normalized ratio (INR). For the majority of patients with VTE, the target therapeutic INR range is 2.0 to 3.0. In patients with cancer, warfarin therapy is problematic because unpredictable anticoagulant response can result from drug interactions, changes in vitamin K status, liver dysfunction, and gastrointestinal disturbances such as vomiting and diarrhea. Furthermore, because vitamin K antagonists have a delayed onset of action and prolonged clearance of the anticoagulant effect, they are difficult to manage in patients who require periodic invasive procedures (eg, therapeutic paracentesis) or who experience frequent episodes of chemotherapy-induced thrombocytopenia.

Cancer patients treated with warfarin also experience frequent recurrent VTE and have a high risk of major bleeding. According to prospective studies, the annual risk of recurrent VTE is 21 to 27% in cancer patients while on warfarin therapy.[23,24] This is 2- to 3-fold higher than in patients without cancer. Recurrent VTE can occur even when the INR is therapeutic (Table 2).[24] Cancer patients on oral anticoagulant therapy also have a risk for major bleeding of 12 to 13%, versus 3 to 4% for patients without cancer (Table 2).[23,24]

Low-Molecular-Weight Heparin

To-date, a number of trials have compared LMWH with vitamin K antagonists for long-term treatment of VTE and two of the trials that studied only cancer patients have been published. The CANTHANOX trial compared 3 months of standard warfarin therapy with enoxaparin in cancer patients with proximal DVT, PE, or both.[25] Only 147 patients were randomized and a statistically significant difference in recurrent VTE and

TABLE 2. The incidence of recurrent venous thromboembolism and major bleeding in relation to the INR[24]

INR Range	Cancer No. of Events (per 100 patient-years)	No Cancer No. of Events (per 100 patient-years)	Total No. of Events (per 100 patient-years)
Recurrent VTE			
≤2.0	54.0	15.9	23.7
2.1-3.0	18.9	7.2	9.2
>3.0	18.4	6.4	8.7
Major bleeding			
≤2.0	30.6	0.0	3.1
2.1-3.0	11.2	0.8	2.6
>3.0	0.0	6.3	5.1

major bleeding was not observed between the groups. After 3 months of treatment, 15 of 71 patients in the warfarin group had recurrent VTE or major bleeding compared with 7 of 67 patients assigned to receive enoxaparin ($P = 0.09$). In a similar patient population, the CLOT trial randomized 676 cancer patients to usual treatment with dalteparin followed by vitamin K antagonist therapy or dalteparin alone for 6 months.[26] In the dalteparin group, patients received therapeutic doses at 200 IU/kg once daily for the first month and then 75 to 80% of the full dose for the next 5 months. Over the 6-month treatment period, 27 of 338 in the dalteparin group and 53 of 338 in the oral anticoagulant group had symptomatic, recurrent VTE. The cumulative risk of recurrent VTE was reduced from 17% in the oral anticoagulant group to 9% in the dalteparin group, resulting in a statistically significant risk reduction of 52% ($P = 0.002$). Accordingly, one episode of recurrent VTE is prevented for every 13 patients treated with dalteparin. Overall, there were no differences in major bleeding or any bleeding. By 6 months, 39% of the patients had died in each group; 90% were due to progressive cancer. Recently, a prospective cohort study showed that a fixed dose of dalteparin 10,000 IU once daily is effective and safe for long-term treatment of VTE in patients with metastatic cancer.[27] Two small randomized trials have compared tinzaparin and enoxaparin with warfarin for long-term use in cancer patients but the full reports have not been published.[28,29] Without further evidence, using these and other LMWHs cannot be recommended at this time and the FDA does not consider various LMWHs as having therapeutic or biochemical equivalence.

Duration of Therapy

Duration of anticoagulant therapy has not been addressed in cancer patients. Based on the accepted concept that the risk of recurrent thrombosis is increased in the presence of any ongoing risk factor, it is generally recommended that patients with metastatic malignancy receive "indefinite" therapy. In patients without metastases, anticoagulant treatment is recommended for as long as the cancer is clinically detectable and while the patient is receiving antitumor therapy. Patients should be reevaluated frequently to assess the risk–benefit ratio of ongoing anticoagulant therapy. Besides the risk of bleeding, the patient's quality of life and life expectancy should be taken into consideration.

Treatment of Recurrent VTE

LMWH has been shown in small case series to be effective in treating patients who develop recurrent VTE while on warfarin therapy.[30] Data

are not available for managing patients who develop recurrence while on LMWH. Options include increasing the dose of LMWH or switching to intravenous or subcutaneous UFH. Studies are needed to address this issue.

Use of Inferior Vena Caval Filters

In patients with proximal DVT, vena caval filters can reduce the short-term risk of PE but can increase the risk of recurrent DVT and postphlebitic syndrome.[31] It is possible that filters are associated with even higher risks of recurrent DVT in cancer patients due to their heightened hypercoagulable state and fatal PE can occur in patients with a filter in place. Therefore, the use of filters should be limited to situations when anticoagulant therapy cannot be used because of serious, active bleeding.

Antineoplastic Potential of LMWHs

Experimental studies have suggested that LMWHs may have anticancer effects and recent clinical trials have shown that LMWH use is associated with a survival benefit, particularly in patients with limited or early-stage malignancy.[7-11] The most compelling evidence comes from two studies. In the MALT study, 302 patients with noncurable solid tumors were randomized to receive nadroparin or placebo for 6 weeks.[9] A statistically significant improvement in median survival was associated with nadroparin. In the Turkish study, 84 patients with newly diagnosed small-cell lung cancer were randomized to receive standard chemotherapy with or without dalteparin.[8] Progression-free survival and overall survival were better in patients who received dalteparin. Although these results need to be confirmed in larger studies and in different tumor types, they do support the concept that activation of coagulation is intrinsically involved in tumor growth and that LMWHs are able to interrupt these critical processes. The exact mechanisms, however, have not been elucidated.

Summary

More than one-third of cancer patients treated with warfarin therapy will develop recurrent VTE and major bleeding. The CLOT trial presents compelling evidence that LMWH dalteparin should replace warfarin and become the standard of care for treatment of VTE in cancer patients. This approach is endorsed by the 7th American College of Chest Physicians Consensus Guidelines.[13] In addition to its superior anticoagulant effect, LMWHs may also provide a survival benefit to patients with cancer. This anticancer potential is being investigated and studies in specific tumor

types are being planned. More studies are also needed to evaluate duration of therapy, bleeding, quality of life, and cost-effectiveness.

Acknowledgment

Dr. Lee is a recipient of a New Investigator Award from the Canadian Institutes of Health Research/Rx & D Research Program.

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Long-Term Anticoagulation Prophylaxis Following Acute Thromboembolism

Thomas M. Hyers, MD

Introduction

Long-term anticoagulation with a vitamin K antagonist (VKA: warfarin and acenocoumarol) is necessary in most patients with venous thromboembolism (VTE), but these drugs present management problems because of their narrow therapeutic range.[1-4] Under-anticoagulation with a VKA (international normalized ratio (INR) $<$ 2.0) increases the risk of thrombotic events, and over-anticoagulation (INR $>$ 4.0) increases the risk of serious bleeding. The narrow therapeutic range of VKAs is further complicated by numerous drug, diet, and metabolic interactions. Consequently, even with highly trained and motivated providers employing frequent monitoring, it is difficult to maintain patients in the targeted INR range.[5]

Because of the practical problems with warfarin management, caregivers and patients together should consider the relative value they place on the risk for both thrombotic occurrence and bleeding. These considerations should begin at the outset of anticoagulation and continue throughout the duration of anticoagulation. In this regard, randomized clinical trials that compared different durations of anticoagulation typically excluded very elderly patients and others whose comorbidity identified high bleeding risk.

Monitoring Therapy

Therapy is monitored by the prothrombin time expressed as the INR. The accepted therapeutic range with the INR is 2.0 to 3.0 for nearly all indications. Clinical trials that targeted an INR below 2.0 have generally shown increased risk of VTE. When the INR remains above 4.0, the risk of serious bleeding, especially intracranial bleeding, increases. There is currently no evidence to support increasing the INR above 3.0, even when

Dis Mon 2005;51:158-165
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.011

TABLE 1. Intensity of chronic anticoagulation with VKAs

Study*	Target INR	VTE Recurrence (%/yr)	Major Bleeding (%/yr)
PREVENT[8]	Placebo	7.2	0.4
	1.5-1.9	2.6	0.9
Kearon[9]	1.5-1.9	1.9	1.0
	2.0-3.0	0.7	0.93

*See text and refs. 8 and 9 for details.

recurrent VTE occurs while a patient's INR has been maintained between 2.0 and 3.0.

Intensity of Therapy

In randomized trials, INR target ranges below 2.0 have failed to demonstrate efficacy comparable to 2.0 to 3.0 in total joint replacement,[6] in stroke prevention in atrial fibrillation,[7] and in long-term secondary prevention of VTE.[8,9] Recently, two studies have been published that addressed the potential benefit of maintaining the INR between 1.5 and 1.9 during long-term anticoagulation after venous thromboembolism. The first study randomized patients to an INR range of 1.5 to 1.9 or to placebo following an initial 6 months of conventional anticoagulation with warfarin at an INR range of 2.0 to 3.0. After a follow-up of approximately 2 years, this study was stopped when the annual recurrence rate was 7.2% in the placebo group compared to 2.6% in the low-intensity INR group.[8] Bleeding rates in the two groups were not significantly different. Patients who suffered recurrence in this study tended to be those with idiopathic disease or thrombophilia. The authors concluded that less intense anticoagulation offered significant benefit to patients for long-term anticoagulation after VTE. The second study randomized patients to either an INR range of 1.5 to 1.9 or 2.0 to 3.0 after 3 months of conventional anticoagulation with warfarin.[9] This study showed an annual recurrence rate of 1.9% in the low intensity group compared to a recurrence rate of 0.7% in the conventional anticoagulation group (Table 1). Taken together, these two studies showed an added benefit of warfarin therapy targeted to an INR range of 2.0 to 3.0.

Apportioning Risk of Recurrent VTE

The risk of recurrence of VTE with long-term anticoagulation has been studied extensively over the last 20 years. Risk can be apportioned over four groups, as follows: (1) patients with a first event and a transient risk factor such as trauma, surgery, or immobilization; (2) patients with a first

TABLE 2. Duration of anticoagulation by risk status

Duration	Patient Risk Group
3-6 months	First VTE with reversible or time-limited risk factor*
6-12 months or longer	First idiopathic VTE
12 months to lifetime	First VTE with
	Cancer
	Antiphospholipid antibody
	Thrombophilia
	Recurrent VTE

*Examples of reversible or time-limited risk factors are trauma, surgical procedures, immobilization, and estrogen use.

event and no identified risk factor (idiopathic or primary VTE); (3) patients with ongoing risk factors such as thrombophilia, antiphospholipid antibody, cancer, or homocysteinemia; and (4) patients with recurrent VTE.

Patients with a first VTE and transient risk factors have the lowest risk of recurrence of the four groups.[10-12] These patients can usually be anticoagulated with a VKA for 3 to 6 months with a very low risk of subsequent recurrence (Table 2). The trials that determined duration in this group compared 4 to 6 weeks to 3 to 6 months of total therapy. Results indicated that shorter duration results in a two- to threefold increase in risk for recurrence compared to a longer duration. However, many of the recurrent events occurred in patients with idiopathic VTE. Findings in the subgroup with a first event and transient risk factors indicated that 3 months of anticoagulation is sufficient. These trials are supported by earlier studies that affixed the duration of anticoagulation in these patients at 3 to 6 months.[13,14]

Patients with idiopathic or primary VTE consistently show a higher risk for recurrence than do those in group 1. Some of these patients have unidentified inherited or acquired risk factors and others have risk factors that are never identified. A number of trials have examined duration of anticoagulation in these patients.[8,15,16] In general, these trials show that anticoagulation should be continued in these patients for at least 6 to 12 months.[15,16] One drawback of these trials is incomplete follow-up of patients in the year after anticoagulation is stopped. With available follow-up data, it appears that no matter how long anticoagulation is continued in this group, recurrence is highest in the 6 to 9 months following discontinuation of therapy. Consequently, decisions about duration of anticoagulation in this group should be based not only on risk of recurrence but also on risk of bleeding, since the latter is a cumulative risk. Benefits of anticoagulation in these patients beyond 1 year begin to

be diluted by the cumulative major bleeding risk that accrues to them (2 to 3%/year). It is the author's approach to recommend 1 to 2 years of anticoagulation in this group and then decide with the patient about further anticoagulation therapy.

Patients with inherited or acquired risk factors for VTE benefit from longer periods of anticoagulation after a first event, although these recommendations are generally based on subgroup analyses of larger trials.[17-21] Recently, a study showed benefit of extended anticoagulation in patients with factor V Leiden or the prothrombin mutation (G21250A).[17] Other groups known to be at high risk include those with deficiencies of antithrombin, protein C or S,[18,19] or combinations of thrombophilic factors.[20] Patients with the antiphospholipid antibody syndrome are at high risk for recurrence.[22,23] A recent study tested two intensities of anticoagulation in patients with the lupus-like anticoagulant.[24] This study showed that an INR range of 2.0 to 3.0 was as effective at preventing recurrence as a range of 3.0 to 4.5. Intensity of anticoagulation in this group should be maintained at an INR of 2.0 to 3.0 and continued for 6 to 12 months after the antibody is no longer detectable.

Patients with VTE and active cancer are known to be at especially high risk of recurrence.[25,26] Recently, a trial compared conventional therapy with a low molecular weight heparin bridging to warfarin (INR 2.0 to 3.0) for 6 months to low molecular weight heparin continued for the full 6 months.[25] This trial showed a 50% reduction in recurrence with no significant increase in bleeding. Mortality rate was about 40% in both groups by the end of 6 months. Regimens that have been used are dalteparin 200 units/kg daily for the first month followed by 150 units/kg daily thereafter, tinzaparin 175 units/kg daily, and enoxaparin 1 mg/kg twice daily for the first 1 to 2 weeks followed by 1.0 mg/kg once daily thereafter. At this time the evidence supports use of LMWH in one of the regimens described above for first 3 to 6 months. After 3 to 6 months of therapy with LMWH, the caregiver and patient should decide together whether to switch to warfarin or continue with LMWH.

Patients with recurrent VTE should receive anticoagulation indefinitely, although no authority has precisely defined indefinitely.[27] Individuals with recurrent VTE require evaluation for inherited and acquired conditions that contribute to recurrent VTE. If a predisposing condition is identified, duration of anticoagulation should be tailored to the particular condition. Patients with two separate VTE occurrences associated with transient risk factors such as surgery or immobilization are particularly

problematic. If no continuing risk factor is identified, it is the author's practice to give anticoagulation to these patients for 2 years after the second event. At that point, a joint decision is made whether to continue anticoagulation. If anticoagulation is stopped, aggressive prophylaxis should be given during any high-risk situation such as surgery or long airplane or automobile trips. If a third episode of VTE occurs, life-long anticoagulation is warranted. Recent studies have suggested that a follow-up venous ultrasound or D-dimer determination may help to assess recurrence risk at the time consideration is being given to stopping anticoagulation.[28,29]

Duration of Treatment of PE versus DVT

There is no evidence to support the notion that patients with pulmonary embolism (PE) should receive anticoagulation for a longer duration than those with deep venous thrombosis (DVT), although patients with pulmonary embolism have a higher mortality rate from recurrent VTE over the next 6 months (1.4% versus 0.4%). About 30% of patients with DVT have symptomatic PE and another 30% have asymptomatic PE. Since PE and DVT are two manifestations of venous thromboembolism, it is generally agreed that the two conditions should be treated similarly with one exception.[4] The exception is the proven benefit of fitted compression hose worn long-term by patients with symptomatic DVT. This adjunctive therapy is described later in this chapter.

Special Situations

Pregnancy is a significant risk factor for VTE with the postpartum period posing the highest risk. Patients who develop VTE during pregnancy should be anticoagulated with a treatment dose of LMWH or UFH. Whichever drug is used, monitoring of therapy is necessary, since pregnancy can alter the clearance of these. With LMWH, an anti-Xa level of 0.5 to 1 unit/mL is desirable at 4 hours after dosing. As the patient on LMWH approaches term, a switch is often made to an anticoagulating dose of unfractionated heparin given subcutaneously twice daily. Unfractionated heparin is preferred at this time because of its faster clearance. Monitoring is again required to achieve a therapeutic APTT throughout at least 8 hours of the dosing interval. Delivery should be accomplished by induction with heparin stopped 12 to 24 hours earlier. Consultation with obstetrician and anesthesiologist is mandatory when planning for delivery in the patients. When hemostasis is achieved after delivery, a treatment dose of LMWH is resumed with a bridge to warfarin for at least 6 weeks postpartum.

Adjunctive Therapy

Three randomized clinical trials have examined the benefit of fitted compression stockings in preventing the postthrombotic syndrome (PTS) after DVT.[30-32] The two largest trials tested fitted hose with a pressure of 30 to 40 mm Hg at the ankle to no hose for 2 years.[30,31] The most recent trial tested fitted hose with a pressure of 20 to 30 mm Hg at the ankle against hose that were two sizes too large.[32] All three trials showed a significant benefit of fitted pressure hose in preventing PTS. At this time evidence supports fitted thigh-high compression hose with a pressure of 30 to 40 mm Hg at the ankle worn for 2 years after an episode of DVT.

Mild findings and complaints characteristic of the postthrombotic syndrome eventually develop in about one-third of patients after a first DVT. Approximately 6% develop severe manifestations such as severe pain, edema, and venous ulcers. Patients can develop this syndrome after proximal or calf vein DVT. Recurrence of DVT in the same leg predisposes to the development of PTS. While fitted compression hose have been shown to reduce the incidence of PTS, there is little reliable data on treatment of the established syndrome. One small study using a crossover design showed that intermittent pneumatic compression with a pressure of 40 mm Hg relieved symptoms in individuals with severe manifestations of PTS.[33] Rutosides given orally have been tested for symptom relief in patients with mild-to-moderate manifestations of PTS. In one small trial with incomplete reporting, rutosides showed some benefit in reducing calf circumference after 4 weeks of therapy.[34] This beneficial effect seemed to be reduced after 8 weeks of therapy. Updated evidenced-based recommendations for treatment of venous thromboembolism and its complications have recently been published.[35]

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Practical Aspects of the Postthrombotic Syndrome

Alessandra Puggioni, MD, Manju Kalra, MBBS, and Peter Gloviczki, MD

Definition and Prevalence

Postthrombotic syndrome (PTS) represents the long-term sequela of deep venous thrombosis (DVT) and is characterized by pain, swelling, varicosity, pigmentation, and skin changes (eczema, induration, ulcers) of the affected lower limb. The estimated incidence of venous stasis syndrome in the U.S. is approximately 150,000 new cases per year; approximately 25% are due to PTS.[1] The exact prevalence of PTS is unknown, but it is proportional to the prevalence of DVT in a certain population. While the incidence of DVT is between 1.0 and 1.6 per 1000 persons per year,[2,3] prospective studies have shown that PTS developed after DVT in 17% of the limbs at 1 year, 23% at 2 years, 28% at 5 years, and in 29% at 8 years.[4]

Classification

The CEAP (Clinical, Etiologic, Anatomic, and Pathophysiologic) classification was formulated a decade ago by an ad-hoc international panel of experts on venous disease; patients were categorized based on their symptoms, physical findings, and diagnostic work-up. An update of the CEAP classification was recently reported.[5]

A detailed description of the CEAP classification is discussed in Chapter 15.

Diagnostic Evaluation

Venous duplex scanning should be performed in all patients with symptoms of chronic venous stasis to define the location, the etiology, and the severity of the underlying problem. Contrast venography is reserved for the more advanced cases, when deep venous reconstructions or endovascular interventions are considered.

Dis Mon 2005;51:166-175
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.012

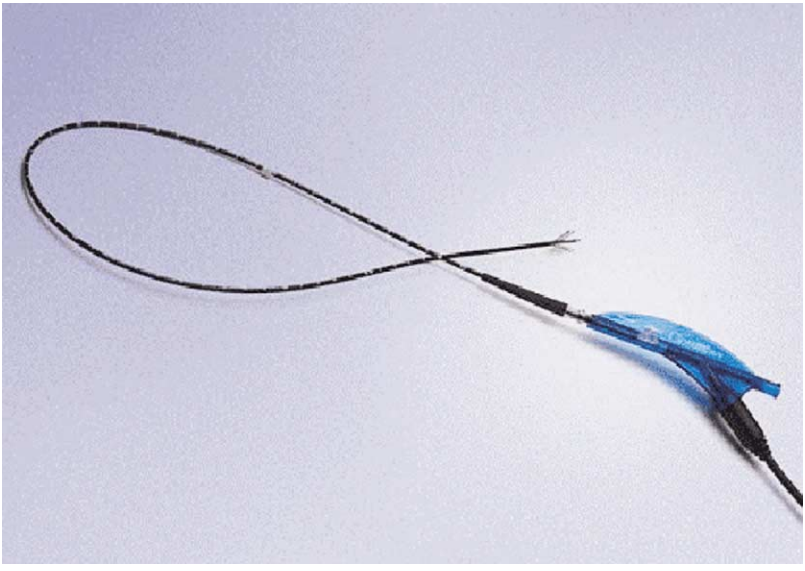

FIG 1. Closure® catheter.

Noninvasive Testing

Duplex scan is used in 2005 to diagnose valvular incompetence and venous obstruction in patients with PTS. Typical appearance of a postthrombotic vein at duplex scan is that of a thickened, hardly compressible vessel with damaged, incompetent valves and variable degrees of venous flow due to partial recanalization. In PTS reflux and obstruction often times coexist, and reflux is frequently a combination of deep and superficial reflux. Duplex scan is an invaluable tool able to identify and quantify the extent of deep, superficial, and perforator vein incompetence.

Air or strain gauge plethysmography is designed to evaluate the global leg hemodynamics by measuring reflux, obstruction, and calf pump function. Decreased vein wall compliance in patients with PTS may interfere with proper evaluation of calf muscle pump function. Unfortunately, the site and the level (superficial, deep, or perforator) of reflux cannot be localized with plethysmography.[6-7]

Invasive Testing

Ascending venography using iodine contrast provides the best "road map" of the deep, superficial, and perforating veins of the limb with

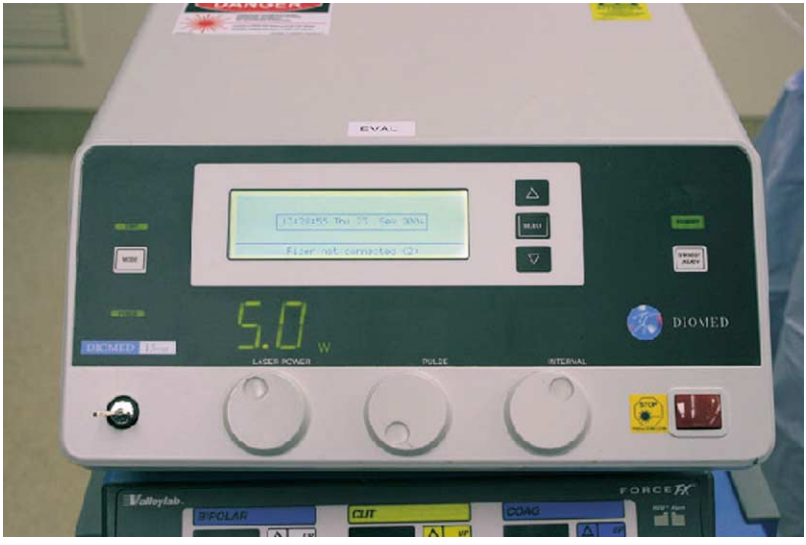

FIG 2. EVLT generator.

localization of the sites of obstruction, collaterals, and patterns of preferential flow.

Descending venography permits evaluation of sites of reflux in the saphenous and deep system under fluoroscopy. Limiting factor is that segments located distal to an obstruction or a competent valve may not be visualized.

It is likely that magnetic resonance venography and computed tomographic angiography will play a more important role in the diagnosis of venous disease in the near future.

Treatment

Conservative Treatment

Symptoms of PTS can be frequently controlled by leg elevation, graduated compression stockings (30 to 40 mm Hg), and local wound care of venous ulcerations. Patient compliance is imperative to maintain effectiveness of conservative treatment.

The benefits of graduated compression stockings reside in their theoretical effects on venous hemodynamics, skin circulation, and calf muscle pump function.[8,9] Randomized prospective studies demonstrated a 50% net risk reduction of developing PTS in patients wearing elastic compression stockings after DVT.[10,11]

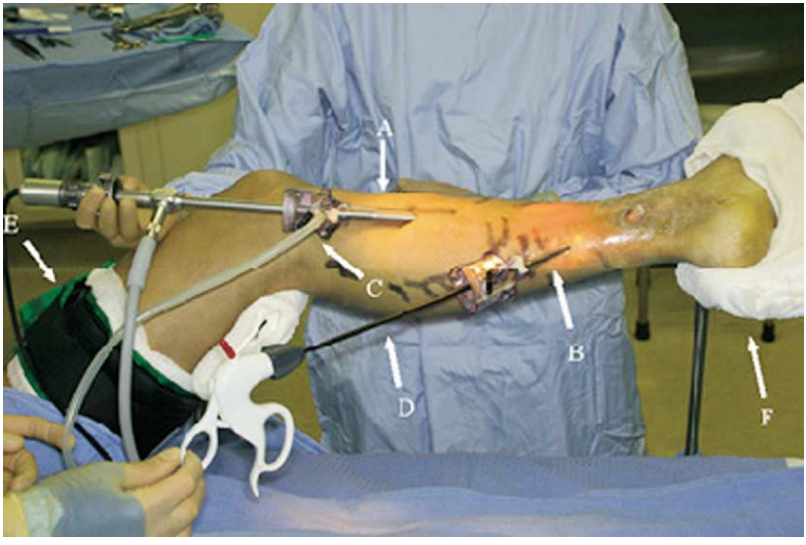

FIG 3. Two port technique of SEPS. One 10-mm port (A) for the camera and a 5-mm port (B) for instrumentation are inserted. Carbon dioxide is insufflated into the subfascial space (C) and pressure is maintained around 30 mm Hg. All perforators encountered are divided with the harmonic scalpel (D). Note the thigh tourniquet (E) and the leg holder (F) to facilitate the operation.

Surgical Treatment

The aim of surgical treatment of PTS is to reduce the ambulatory venous hypertension secondary to obstruction and/or reflux in the deep, superficial, and perforating systems. Ablation of the saphenous reflux alone may be beneficial in this group of patients.[12]

The recent trend toward minimally invasive surgery has led to the development of percutaneous means of ablating the great saphenous vein with radiofrequency (Closure®) (Fig 1) or laser energy (Endovenous Laser Therapy, EVLT) (Fig 2). In a series of patients with leg ulcers treated by EVLT reported healing rate was 83%.[13] Although most large studies using EVLT or Closure® treatment are performed in patients with primary and not postthrombotic varicosity,[14,15] it is likely that their effectiveness in PTS will match or come close to the results obtained with saphenous vein stripping. Few reports, including one from our institution, raised concerns about the possibility that these new endovenous techniques may occasionally be complicated by extension of saphenous thrombus into the femoral vein[16,17]; strict follow-up with early duplex scanning and periprocedural anticoagulation should be considered in this patient population.

Subfascial endoscopic perforator vein surgery (SEPS) is a minimally

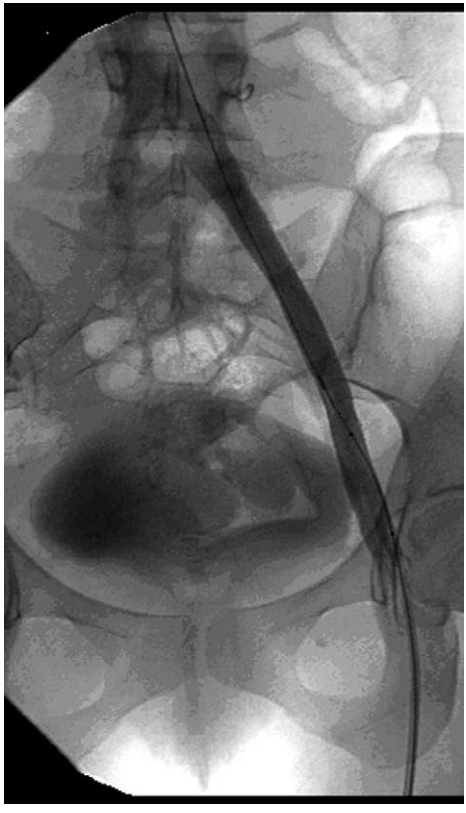

FIG 4. Angioplasty and stenting of left CIV and EIV. Angiogram at the end of the procedure shows resolution of obstruction.

invasive technique aimed to interrupt incompetent perforators using endoscopic instrumentation (Fig 3). This procedure is associated with satisfactory early outcome in PTS (72% healing rate at 90 days), but ulcer recurrence is high (56% at 5 years versus 15%).[18] Thus, the role of SEPS in this group of patients remains controversial. Duplex-guided sclerotherapy of the perforating veins has been used for PTS with good results.[19]

Postthrombotic valves are rarely amenable to direct surgical repair, but primary valvular incompetence in patients with associated PTS can be treated with external or internal valvuloplasty,[20,21] although long-term success is less satisfactory than in primary disease.[22] Transplantation of autologous upper extremity vein segments (axillary, brachial, or basilic) can be employed to replace postthrombotic segments in the lower extremity.[23] Patients with incompetent valve stations below the groin may benefit from a valve transposition procedure. With this technique the

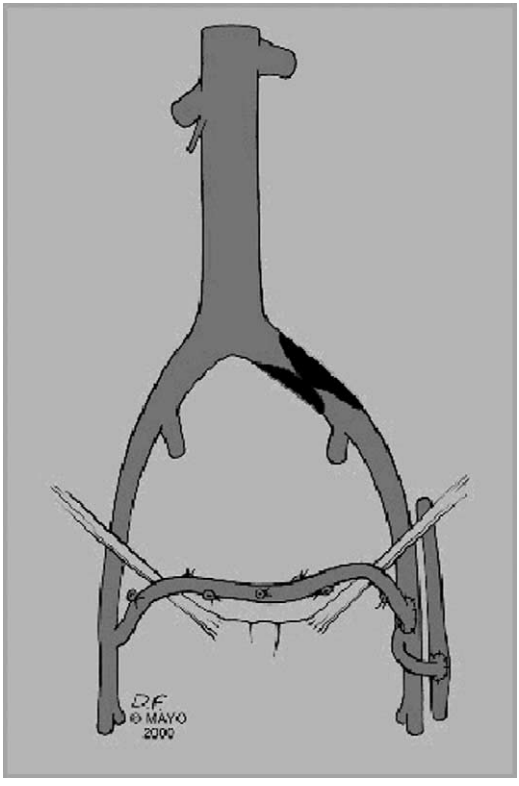

FIG 5. Illustration of Palma-Dale femoro-femoral saphenous transposition. A distal arteriovenous fistula (right) can be added to improve patency.

incompetent femoral vein is ligated and the distal end is anastomosed to a competent saphenous or profunda vein.[24]

Occlusion or stenosis of the iliac vein can be effectively treated today with percutaneous stents (Fig 4). Primary and secondary patency rates of 71 and 90%, respectively, have been reported at 2 years.[25,26] If the patient with unilateral iliac vein occlusion is not a candidate for stents or failed previous stenting procedures, a crossover saphenous vein transposition (Palma–Dale operation) can be attempted. With this technique the contralateral saphenous vein is harvested and anastomosed to the femoral vein distal to the obstruction (Fig 5). Patency rates over 80% at 5 years have been reported.[27,28] Iliocaval obstructions are also amenable to iliocaval (Fig 6) or femorocaval ePTFE bypass grafts; in our experience secondary patency rate at 2 years of 54% can be achieved, with frequent use of a femoral arteriovenous fistula.[28]

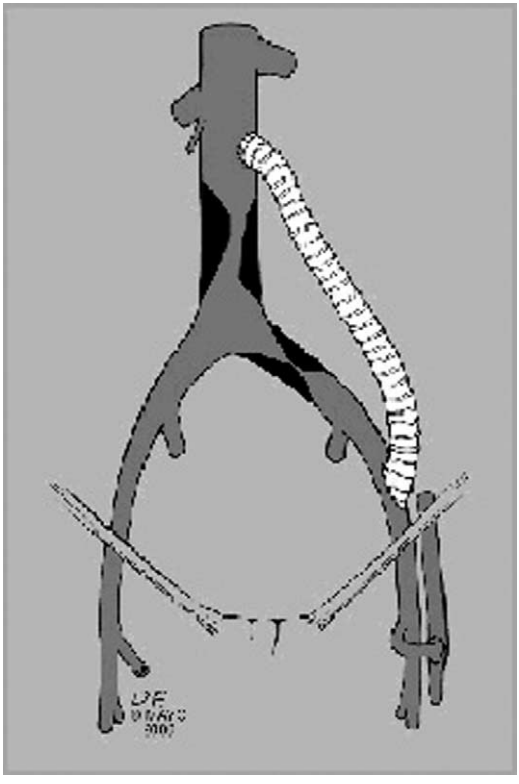

FIG 6. Illustration of iliocaval bypass with ringed PTFE graft and a left femoral arteriovenous fistula.

Patients with left-sided acute DVT frequently have chronic obstruction of the iliac vein, caused by the overriding right common iliac artery (May–Thurner syndrome); thrombolysis or sometimes surgical thrombectomy in these patients should be combined with an attempt at stenting of the left iliac vein.[29,30] In patients with postthrombotic syndrome surgical treatment of the occluded or incompletely recanalized femoral vein using the "endophlebectomy" technique can be effective alone or used as an adjunct to stenting (Fig 7).[31]

Future Perspectives

EVLT and Closure will be used more frequently for PTS to treat saphenous incompetence. Biological valves, such as autogenous and cryopreserved grafts, have been used in animal studies with partial success due to early thrombosis and loss of competence.[32,33] Cryopreserved monocusp patches

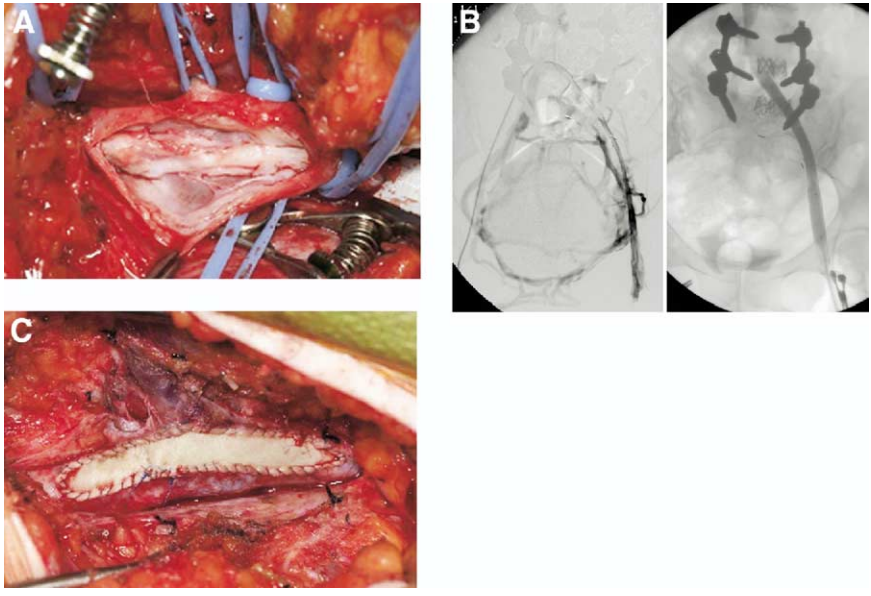

FIG 7. (A) Chronic femoral vein thrombosis in a patient with postthrombotic syndrome. (B) Endophlebectomy was followed by iliofemoral stenting (pre- and poststenting venograms) and (C) a patch angioplasty of the femoral vein using bovine pericardium.

made from cadaveric pulmonary arteries have been successful in correcting primary valvular insufficiency of the common femoral vein in patients with chronic venous ulcers, but no data on PTS are available.[34]

Among percutaneously implanted artificial venous valves, the small-intestinal submucosa square-stent bicuspid venous valve has shown very promising results. In long-term experimental studies in sheep with valves placed into the jugular vein only 12% had decreased function because of valve tilting and 4% had partial thrombosis in the tilted valve.[35] Early and mid-term results of iliac stents have been very encouraging and further improvement can be expected using drug eluting stents and new adjuvant treatments in the future. Minimally invasive endovenous and endoscopic treatments hold promise to decrease morbidity and disability of patients with postthrombotic syndrome and venous ulcers.

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CEAP Classification for Chronic Venous Disease

Frank T. Padberg, Jr, MD

Introduction

Evaluation of chronic venous disorders (CVD) was dramatically improved with the worldwide acceptance and dissemination of the CEAP classification. Thoughtful description provides better understanding, which is reflected in improved management of CVD.

Previously, terms were not uniformly defined and their meaning differed from practitioner to practitioner, from practice to practice, from institution to institution, and from country to country. The establishment of a uniform language for classifying the findings of CVD in North America began with the Committee on Standards established by the Society for Vascular Surgery and the International Society for Cardiovascular Surgery. The original publication[1] and its revision by an international consensus committee appeared in the *Journal of Vascular Surgery* in 1995.[2] These included detailed descriptive recommendations for venous thromboses, pulmonary emboli, and upper extremity VTE in addition to a uniform description of CVD limbs. A concise three-point disability score was also included.

In addition to a classification, better estimates of disease severity were also needed. A clinical severity score developed at this international consensus conference became a common feature of manuscripts on CVD, but was somewhat unresponsive to change.[3] In 2000, the outcomes committee of the AVF developed and published a revised Venous Clinical Severity Score (VCSS), accompanied by an anatomic score, and a more versatile modification of the disability score.[4] While each of these was focused on physician assessment, the patient's perception was emphasized by disease-specific questionnaires reflecting their quality of life.

One decade following the original consensus conference, its sponsor,

Note. Additional information is available at the American Venous Forum web site: americanvenous-forum.com, dvt-info.com, or venous-info.com.

Dis Mon 2005;51:176-182
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.013

TABLE 1. Basic CEAP Classification — Clinical, Etiologic, Anatomic, Pathophysiologic

C-Clinical Class	Characteristics*	
0	No clinical findings or symptoms	**E-Etiology****
1	Telangiectasia or reticular veins	C Congenital
2	Varicose veins	S Secondary
3	Edema, only due to a venous etiology	P Primary
4	(a) Pigmentation and/or eczema	**A-Anatomy****
	(b) Lipodermatosclerosis, atrophie blanché	S Superficial
5	Prior ulceration, now healed	P Perforator
6	Active ulceration.	D Deep
A,S	Subscript: Asymptomatic, Symptomatic	
		P-Pathophysiology**
Date	Date of investigation	R Reflux
Level	Level of investigation (I,II,III)	O Obstruction
		R-O Both
		N** No evident disease**

*Complaints are expected to be related to venous insufficiency and are not classified if another etiology is present (ie, edema secondary to heart failure).
**The N subscript indicates no evidence of disease. It is applicable to E, A, and/or P of CEAP.

the American Venous Forum (AVF), convened a new international group to consider revision of the CEAP classification.[5] The revised classification includes a less complex reporting option (basic CEAP) and increased flexibility. Publication of these documents in multiple international journals and widespread acceptance of the classification have resulted in international uniformity of the current literature focused on venous problems.

The Clinical Classification C $1,2,3,4,5,6\&0_{(A,S)}$

The clinical classification is the foundation of the concept. The six CVD categories range from small thread-like veins to edema, discoloration, induration, and ulceration. Each is clearly defined as noted in Table 1. C-0 is provided for the designation of no clinical findings of venous disease. C-0 is appropriate for those individuals with objective evidence of venous disease (ie, E, A, and/or P), but with no clinical manifestations. The 2004 revision recommends that the criterion differentiating a reticular vein and a varicose vein be defined as a diameter of >3 mm in diameter.[5] The extent of varicose disease along with the other clinical findings are categorized in the severity score.[4] In addition, clinical class 4 is now subdivided into (a) pigmentation and/or eczema, and (b) lipodermatosclerosis and/or atrophie blanche, based upon observational survey data suggesting that lipodermatosclerosis or atrophie blanche (4b) was more likely to progress to more severe disease.[5,6]

Subscripts are applied to designate S (symptomatic) from A (asymptomatic) limbs. Complaints qualifying for the S subscript include ache, pain, tightness, skin irritation, heaviness, muscle cramps, and other complaints that may be attributable to venous dysfunction. While most of these diffuse and nonspecific symptoms have historically been attributed to CVD, recent investigations from the Edinburgh Vein Study and the VEINES studies have cast substantial doubt on the reliability of these assumptions.[7,8] Thus, even though the revised classification will accept these as possibly related to a venous etiology, the practitioner is advised to use his own judgment before attempting to correct anatomic problems which may, in fact, have very little to do with a patient's complaints.

Data limited to clinical evaluation provide only a Level I investigation. Clearly, even the most basic CEAP classification requires accurate assignment of the EAP components; characterization with a duplex study accurately defines these components and defines the more objective Level II evaluation. More extensive investigations with magnetic resonance, computed tomography, or phlebography are designated Level III and will become more commonplace. Recording the date of CEAP assignment facilitates longitudinal comparisons.

Similar in concept to the C0 classification, a subscript of no disease found (N) is provided for E, A, and P classifications. N is for patients whose physical findings rate clinical classification, but who have no objective or historical evidence of venous disease (i.e. E, A, or P are normal).

Etiology ($E_{C,P,S,N}$)

Four categories are included in this classification: Congenital, Primary, Secondary, and None. While arteriovenous malformations represent an obvious congenital (C) etiology, it may also include uncommon conditions such as avalvulia (hereditary absence of venous valves).

Secondary (S) designates any known cause of the venous abnormality. Most commonly, secondary will indicate veins that have been affected by thrombosis. Trauma and prior surgical alteration would also qualify.

Primary (P) essentially refers to all others. Usually this indicates primary valvular reflux.

A subscript designation of (N) is also appropriate for no evident etiology of CVD.

TABLE 2. Advanced CEAP: specific anatomic segment designations

No.	Superficial	No.	Deep Venous System
1	Telangiectasis/reticular veins	6	Inferior vena cava
2	Great saphenous vein (AK)	7	Common iliac vein
3	Great saphenous vein (BK)	8	Internal iliac vein
4	Small saphenous vein	9	External iliac vein
5	Nonsaphenous veins	10	Pelvic: gonadal, broad ligament veins, other
		11	Common femoral vein
	Perforating Veins	12	Deep femoral vein
17	Thigh perforators	13	Femoral
18	Calf perforators	14	Popliteal
		15	Crural: AT, PT, peroneal
		16	Muscular gastrocnemial, Soleal veins, other

AK, Above Knee; BK, Below Knee; AT, Anterior Tibial; PT, Posterior Tibial.

Anatomy ($A_{S,P,D,N}$)

There are two options in this category—Basic and Advanced. Basic CEAP assigns a limb to one or more of the three commonly recognized anatomic venous systems in the limb—superficial, perforating, and deep veins. For general use, simple designation of one (or more) of the three major lower extremity anatomic venous systems is sufficient to localize the site of the abnormality and will probably influence treatment recommendations (Table 1). The superficial system includes the great and short saphenous systems as well as any branch varices. Perforating veins communicate between the superficial and deep systems. The deep system includes the calf veins and sinuses, popliteal, femoral, iliac veins, and vena cava.

Advanced CEAP specifically designates the anatomic location of the venous abnormality and is intended for precise reporting. The numeric designations for specific anatomic sites are listed in Table 2.

A subscript designation of (N) is also appropriate for no evident disease. For example, minimal anatomic findings are commonly observed in morbidly obese individuals with severe, recalcitrant clinical findings.[9] Here the absence of the usual anatomic components is replaced with what may be a problem of relative obstruction from intraabdominal pressures.

Pathophysiology ($P_{R,O,R\text{-}O,N}$)

The two major categories—Reflux (R) and Obstruction (O)—are not mutually exclusive; they may occur alone or in combination (R-O). Reflux is defined as reverse flow with a duration of >0.5 sec by duplex

analysis. Ideally, obstruction is defined objectively by imaging or noninvasive testing. For example, visualization of an occluded vein segment as in acute thrombosis or prolonged outflow on a plethysmographic study provides confirmation of diagnosis.

A subscript designation (N) is again appropriate.

Assessment of Severity and Disability

The descriptive clinical classification, while intended to be hierarchical, was not designed as a severity score. However, it does provide a framework for the VCSS, thus retaining consistency and continuity in the evaluation of the limb with CVD. To determine severity of disease, a venous clinical severity score (VCSS), a disability score, and several disease-specific quality-of-life questionnaires are available. While the details of physician- and patient-oriented severity assessment are beyond the scope of this monograph, a brief description is included for those seeking greater familiarity.[4,8]

Clinical Severity Scoring

The clinical severity score reflects the physician's or nurse's structured opinion regarding the effect of the disease on the patient. Revision of the clinical severity score emphasized common clinical findings that were expected to change and improve (or deteriorate) during the course of clinical observation and treatment.[4] The revised version has now been field tested and found to have reasonable reproducibility.[10,11] The venous clinical severity score was designed to integrate directly with the clinical classification and is heavily weighted toward the most severe aspects of CVI—ulceration, swelling, and infection. Based on a maximal score of 30, disease is considered relatively severe in patients who generate scores greater than 8.

Disability Scoring

The disability score offers a straightforward summary based upon the individual's capacity to live with their CVI. On a scale of 0 to 3, the clinician grades the individual's capacity to negotiate the activities of daily life with or without the aid of a high-quality, graduated compression garment. This assessment also correlates well with the VCSS and the clinical classification.[10,11]

Quality-of-Life Assessment

The patient's perspective is appropriately becoming an increasingly important measure in the assessment of treatment outcomes. While

clinicians pride themselves on astute diagnosis and objective measures of improvement, the perceived value of the treatment to the patient is really the most important final opinion. This evaluation may be of even greater importance when the severity scale registers lesser numbers. Individuals whose primary reason for seeking treatment in class 1 and class 2 CVD may not have extensive physiologic abnormalities and more subtle complaints may be elucidated by these questionnaires.

Although detailed scoring is generally beyond the realm of most nonspecialty practices, the concept has found wide utility in other common measures such as the depression screen. It is generally recommended that both a generic and a disease-specific questionnaire be administered. Such information helps the clinician determine if the complaints are related to environmental factors unrelated to corporeal disease. Questionnaires are available for general evaluation of CVI as well as those specifically designed for evaluation of varicose veins and ulceration.[4]

Summary

This classification is targeted at all forms of venous insufficiency. The utility of a uniform classification and severity grading system permits more accurate and meaningful dialog between the generalist practitioner, the specialist, and the patient. These questions and scores provide a means to assess severity at a given point in time as well as the improvement or deterioration accompanying treatment.

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Perioperative Bridging Therapy for the At-Risk Patient on Chronic Anticoagulation

Alex C. Spyropoulos, MD, FACP, FCCP

Introduction

The management of at-risk patients receiving long-term oral anticoagulant (OAC) therapy that requires temporary discontinuation for an elective surgical or invasive procedure remains problematic and complex. While OAC therapy during surgery is associated with increased bleeding, discontinuation and resumption of OAC—specifically warfarin—will take days before its antithrombotic effect is realized, potentially placing the patient at increased risk of thromboembolism (TE), especially in the postoperative period. Multiple factors play a role in the perioperative management of the patient on chronic OAC, including the bleeding and thromboembolic risks of the patient and surgical procedure, the thromboembolic risks of discontinuing OAC, the use of perioperative bridging therapy, and health-care utilization. This review will outline these factors and provide a management strategy for the at-risk patient on chronic OAC requiring temporary discontinuation for an elective surgical or invasive procedure, with emphasis on the indications for use of perioperative bridging therapy. The term "bridging therapy" will refer to the use of parenteral, short-acting anticoagulants such as unfractionated heparin (UFH) or low-molecular-weight-heparin (LMWH) during subtherapeutic levels of OAC in the perioperative period.

Thromboembolic and Bleeding Risks in the Perioperative Period

With regards to optimal perioperative management of the patient on chronic OAC, patient (intrinsic) and surgical/procedural (extrinsic) risk factors for both thrombosis and bleeding need to be assessed and appropriately risk stratified. Thromboembolic risks include disease-specific thromboembolic risks when discontinuing warfarin, possible

Dis Mon 2005;51:183-193
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.014

hypercoagulability associated with warfarin discontinuation itself, and hypercoagulability associated with surgery. Bleeding risks include those associated with the patient, the use of anticoagulant therapy, and the surgery or procedure itself. Last, thromboembolic risk reductions with the use of OAC as well as clinical consequences of thromboembolic and bleeding events need to be factored.

Thromboembolic Risk When Discontinuing Warfarin

For venous thromboembolism (VTE), it is estimated that, in the absence of OAC during the first month of an acute VTE event, the risk of recurrence is 40%, while it is 10% during the second and third months of treatment.[1] The overall risk of recurrence is much lower after 3 months of OAC treatment, estimated at 15%/year.[1] In addition, acquired hypercoagulable states such as the antiphospholipid syndrome and malignant neoplasms, and congenital thrombophilias such the Factor V Leiden mutation, are independent risk factors for recurrence.[2-4]

For arterial thromboembolism (ATE), patients with nonvalvular atrial fibrillation (NVAF) are at increased risk of stroke in the absence of OAC.[5] One validated clinical prediction score, the $CHADS_2$, uses the following risk factors to estimate expected stroke rate per 100 patient-years: recent congestive heart failure, hypertension, age of at least 75 years, diabetes mellitus, and history of stroke or transient ischemic attack.[6] Moderate-risk patients have an adjusted stroke rate of up to 5.9 (95% CI 4.6 to 7.3), whereas high-risk patients have adjusted stroke rates of 8.5 (6.3 to 11.1) to 18.2 (10.5 to 27.4).

Patients with mechanical prosthetic cardiac valves (MHV) are at increased risk of systemic embolization—manifested as stroke or myocardial infarction—and occlusive thrombus of the orifice of the prosthetic valve during subtherapeutic levels of OAC, especially when the International Normalized Ratio (INR) falls below 2.0.[7] In the absence of OAC, mitral position valve prostheses have an annualized thrombosis risk of 22% compared with an annualized risk of approximately 10 to 12% for aortic position valves.[8] Caged-ball and tilting-disc valves (Starr-Edwards, Bjork-Shiley) have a greater thrombotic risk than bileaflet valves (St Jude).[8] Thus, patients with first-generation valve types, mitral position valves, and prosthetic valves with other risk factors for embolization (such as NVAF, prior embolic event, severe left ventricular dysfunction, and an underlying hypercoagulable state), are considered at high risk for TE in the absence of OAC.[9]

There is a well-described prothrombotic effect of major surgery and laparoscopic procedures,[10,11] while it is estimated that surgery will

theoretically increase the postoperative VTE risk 100-fold.[1] There is also accumulating evidence that surgery may increase the risk of ATE,[12] and a recent systematic review revealed a 10-fold greater risk of stroke than expected in patients not receiving perioperative anticoagulation.[13] Last, although controversial, there are some data to suggest that abrupt discontinuation of warfarin causes more thrombotic events than gradual, or stepwise, reduction.[14]

Bleeding Risks Associated with the Patient, Procedure, and Anticoagulant Therapy

A patient's previous history of bleeding, especially with invasive procedures or trauma, is an important determinant in assessing surgical bleeding risk, as is use of concomitant antiplatelet and nonsteroidal antiinflammatory medications. Procedural bleeding risks in terms of anticoagulant bridging have been identified as high risk or low risk by various surgical or subspecialty societies and bridging management studies.[15,16,17] Surgical procedures that appear to have a high bleeding risk include major operations and procedures (lasting >45 minutes) such as heart valve replacement, head and neck cancer surgery, bilateral knee replacement, and kidney biopsy, whereas procedures with a low bleeding risk include non-major operations and procedures (lasting <45 minutes) such as abdominal hysterectomy, cutaneous procedures, and cholecystectomy.[15] A reasonable estimate of increased major bleeding with the use of perioperative anticoagulants over a 2-day period is 2 to 4% for major surgery and 0 to 2% for non-major surgery.[18]

Thus the bleeding and thrombotic risks for a particular patient on chronic OAC with a given surgery or invasive procedure, given the previously elucidated factors, can be risk stratified into the scheme described in Table 1. Although the thromboembolic risk categories defined as high, intermediate, and low have not been prospectively validated and may have some overlap, there is considerable usefulness in their designation in developing a bridging strategy. The estimated thromboembolic risk reduction with the use of OAC for various indications varies from approximately 65 to 80%.[1] Last, the clinical consequences of a thrombotic or bleeding event must be taken into consideration: MHV thrombosis is fatal in 15% of patients; ATE results in death or major disability in 70% of patients, while VTE has an estimated permanent death or disability rate of approximately 5%, and postoperative major bleeding has a fatality rate of approximately 3%.[18-20]

TABLE 1. Thromboembolic and procedural bleeding risks when discontinuing OAC for a surgical or procedural intervention

	Thromboembolic Risk*		
	High	**Intermediate**	**Low**
Bleeding risk			
Low	A	B	C
High	D	E	F

A. Thromboembolic risk when discontinuing OAC[6,9,24,33]

High (annual ATE risk >10%; 1-month VTE risk >10%)
VTE within 1–3 months
NVAF $CHADS_2$ score 4–6 or AF with MHV or stroke
MHV mitral position
Prosthetic heart valve with other risk factors (prior TE, AF, severe left ventricular dysfunction, or known hypercoagulable state) or recently placed (<3 months)
MHV with older valve model (caged-ball; tilting-disc)
NVAF with clinically apparent rheumatic heart disease
Intracardiac thrombus
TE event with known hypercoagulable state (Protein S or C deficiency, antithrombin deficiency, homozygous factor V Leiden mutation, antiphospholipid syndrome, active cancer) or recurrent idiopathic TE
Intermediate (annual ATE risk 5–10%; 1-month VTE risk 2–10%)
VTE >3 <6 months
MHV aortic position without risk factors
NVAF $CHADS_2$ score 2–3
Recurrent stroke/transient ischemic attacks without risk factors for cardiac embolism
Low (annual ATE risk <5%; 1-month VTE risk <2%)
Remote VTE >6 months
NVAF $CHADS_2$ score 0–1
Intrinsic cerebrovascular disease without recurrent strokes/transient ischemic attacks

B. Procedural Bleeding Risks**[15-17,27]

High (2-day risk of major bleed 2–4%)
Heart valve replacement
Coronary artery bypass
Abdominal aortic aneurysm repair
Neurosurgical/urologic/head and neck/abdominal/breast cancer surgery
Bilateral knee replacement
Laminectomy
Transurethral prostate resection
Kidney biopsy
Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
PEG placement
Endoscopically guided fine-needle aspiration
Multiple tooth extractions
Vascular and general surgery
Any major operation (procedure duration >45 minutes)
Low (2-day risk of major bleed 0–2%)
Cholecystectomy
Abdominal hysterectomy

TABLE 1. Continued

	Thromboembolic Risk*		
	High	**Intermediate**	**Low**
B. Procedural Bleeding Risks[15-17,27] **(continued)**			
Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endonosonography without fine needle aspiration			
Pacemaker and cardiac defribillator insertion and electrophysiologic testing			
Simple dental extractions			
Carpal tunnel repair			
Knee/hip replacement and shoulder/foot/hand surgery and arthroscopy			
Dilatation and curettage			
Skin cancer excision			
Abdominal hernia repair			
Hemorrhoidal surgery			
Axillary node dissection			
Hydrocele repair			
Cataract and noncataract eye surgery			
Noncoronary angiography			
Bronchoscopy ± biopsy			
Central venous catheter removal			
Cutaneous and bladder/prostate/thyroid/breast/lymph node biopsies			

*Includes theoretical 100-fold postoperative VTE risk with major surgery.
**Based upon definitions derived from surgical/subspecialty societies during anticoagulant bridging or management studies in bridging therapy.

Perioperative Bridging Therapy—Clinical Studies

A recent systematic review concluded that chronically anticoagulated patients undergoing non-major procedures such as dental procedures, joint and soft-tissue injections and arthrocentesis, cataract surgery, and upper endoscopy and colonoscopy with or without biopsy can undergo the procedure without alteration of their OAC.[13] Although a concern exists as to the efficacy of LMWH in preventing stroke in patients with NVAF,[21] observational cohort studies involving relatively small patient numbers indicate that outpatient-based treatment-dose LMWH bridging therapy was associated with low thromboembolic and bleeding complications in patients on chronic OAC for mostly arterial/MHV indications undergoing mostly non-major procedures.[22-24] More recent, larger prospective cohort studies and registries of patients on chronic OAC with ATE (including high-risk NVAF and MHV) and high-risk VTE that required bridging therapy with mostly LMWH for both major and non-major elective procedures have been completed.[15,25-27] These studies reveal an overall thromboembolic complication rate of 0.6 to 3.6% and an overall major bleed rate of 0.9 to 6.7%, although there was heterogeneity in study designs, patient populations, LMWH regimens, and outcome definitions. The two LMWHs studied in this

setting were enoxaparin (Sanofi-Aventis, Bridgewater, NJ) and dalteparin (Pfizer, La Jolla, CA). The study by Kovacs and coworkers and preliminary data from PROSPECT indicate that treatment dose LMWH as bridging therapy is feasible and associated with few episodes of thromboembolism. However, PROSPECT revealed that once-daily treatment-dose LMWH is associated with an increase in major bleeding in major surgery versus non-major surgery (21.6% versus 0.7%). The large registry by Douketis and coworkers revealed that a standardized periprocedural anticoagulant regimen with twice-daily LMWH as bridging therapy is associated with low thromboembolic and major bleeding complication rates (0.62% [0.17 to 1.57] and 0.92% [0.34 to 2.00], respectively), provided that postoperative LMWH bridging was not used in a priori defined high-bleeding risk procedures.[15] Preliminary data from REGIMEN, a large multicenter registry of LMWH versus UFH as perioperative bridging therapy in patients on chronic OAC, concluded that bridging therapy with LMWH in selected outpatients appears at least as safe and effective as in-hospital bridging therapy with UFH. Univariate analysis revealed that postoperative prophylactic-dose heparin (either UFH or LMWH) was associated with a 63% reduction in minor bleed events ($P < 0.01$), while multivariate regression analysis revealed that postoperative use of LMWH versus UFH was associated with a trend toward reduction in major bleeding (OR 0.76 [0.32 to 1.81]).

Patients with MHVs requiring bridging therapy with heparin are an especially high-risk group, from a thromboembolic point of view. Table 2 summarizes the clinical studies of the use of UFH or LMWH as bridging therapy for this group of patients. Although some prior controversy existed as to the efficacy of LMWH in patients with MHV, especially in the setting of pregnancy, these studies and preliminary data from subgroup analyses of large registries using LMWH as bridging monotherapy indicate an overall low TE complication rate of $<1.0\%$.[15,27,28]

Last, emerging pharmacoeconomic studies indicate the possibility of substantial cost savings and reductions in healthcare utilization with mostly outpatient-based bridging strategies of patients on chronic OAC using LMWH versus in-hospital bridging with UFH. Regression analysis from REGIMEN showed a significant 56% reduction in hospital length-of-stay with the postoperative use of LMWH versus UFH, while another study revealed significant mean cost savings of over $13,114 in the LMWH group versus UFH group during a 40-day episode of care.[27,32]

TABLE 2. Studies in UFH and LMWH as perioperative bridging therapy in patients with MHVs

	MHV (total *n*)	Bridging Strategy	TE Events (%)	Major Bleeds (%)
Katholi 1978[29]	235	Mitral-Post-IVUFH* Aortic-Post-none	0	3 (1.2)
Spandorfer 1999[22]	12 (20)	Pre-Enox BID** Post-Enox BID	0	0
Montalescot 2000[30]	208	Post-IVUFH Post-mostly Enox BID	1 (0.94) 0	2 (1.9) 2 (2.0)
Tinmouth 2001[23]	12 (24)	Pre-Dalt QD† Post-Dalt QD	1 (8.3)	0
Ferreira 2003[31]	82	Pre-Enox BID Post-Enox BID	0	1 (1.2)
Spyropoulos 2004[24]	28 (84)	Pre-Enox BID Post-Enox BID	0	2 (7.1)
Douketis 2004[15]	215 (650)	Pre-Dalt BID Post-Dalt BID/none	1 (0.46)	1 (0.46)
Kovacs 2004[25]	112 (224)	Pre-Dalt QD Post-Dalt QD/Dalt 500U/none	5 (4.5)	8 (7.1)
Turpie 2004[28]	174	Pre-Enox BID Post-Enox BID	1 (0.56)	4 (2.3)
Spyropoulos 2004[27]	246 (1077)	Post-IVUFH Post-mostly Enox BID	1 (1.5) 0	5 (7.5) 7 (4.2)
Total	1324		10 (0.75)	35 (2.6)

*IVUH denotes dose-adjusted intravenous unfractionated heparin to an activated partial thromboplastic time of 1.5–2.5 times control.
**Dose of the LMWH enoxaparin is 1 mg/kg SQ BID.
†Dose of the LMWH dalteparin is 100 IU/kg SQ BID, 200 IU/kg SQ QD, or 5000 IU SQ QD.

Perioperative Management Recommendations for Bridging Therapy of the At-Risk Patient on Chronic OAC

The Seventh American College of Chest Physician Consensus Conference recommends the use of prophylactic (or higher) dose UFH or LMWH as perioperative bridging therapy in patients considered at intermediate risk of thromboembolism, and full-dose UFH or LMWH as perioperative bridging therapy in patients considered high risk of TE (including a history of VTE <3 months, MHV in the mitral position, and old-model cardiac valve).[8] For patients with a low risk of bleeding, the recommendation is to continue warfarin therapy at a lower dose to maintain an INR of 1.3 to 1.5. All are Grade 2C recommendations.

Based upon the available data of perioperative thrombotic and bleeding risks and clinical studies using UFH and LMWH as bridging therapy, a more explicit bridging algorithm for high and intermediate TE risk patients is shown in Fig 1. OAC should be discontinued at least 4 days prior to the

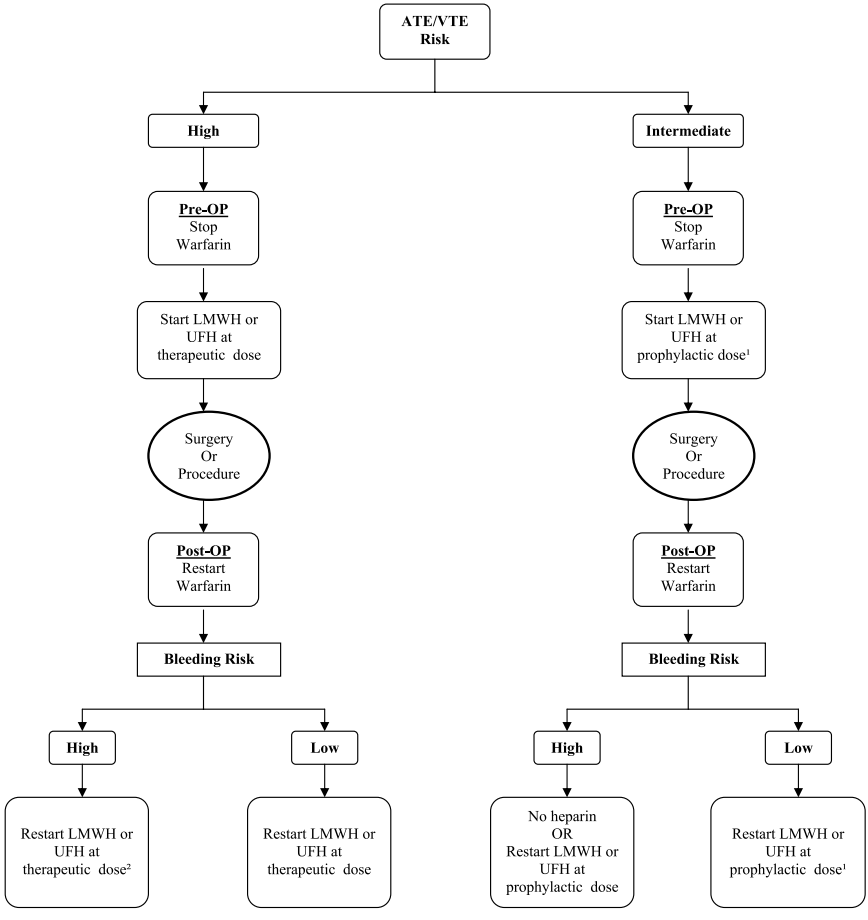

FIG 1. Perioperative bridging algorithm for patients at high or intermediate risk of thromboembolism. For patients with a low risk of ATE or VTE, recommendation is no heparin bridging preoperatively and only prophylactic doses of LMWH or UFH postoperatively in conjunction with resumption of warfarin. (1) Some experts would recommend treatment-dose LMWH or UFH preoperatively for this group of patients. Prophylactic dose UFH includes UFH 5000U SQ BID/TID and prophylactic dose LMWH includes enoxaparin 30 mg SQ BID or 40 mg SQ QD, or dalteparin 5000U SQ QD. (2) Recommend waiting at least 24 hours before reinitiation of bridging therapy. Some experts would advocate the use of prophylactic dose LMWH or UFH in this setting.

surgical intervention or procedure, with heparin (either UFH or LMWH) initiated at least 2 days prior to the intervention. While many experts would advocate preoperative therapeutic-dose UFH or LMWH for intermediate- to high-risk patients, there is considerable disagreement as to whether a prophylactic dose, treatment dose, or no heparin bridging therapy should be initiated postoperatively in conjunction with resumption of OAC, depending

TABLE 3. Perioperative bridging protocol for patients on oral anticoagulation requiring therapeutic-dose (LMW) Heparin

Instructions regarding warfarin use
1. Stop warfarin at least 4 days prior to surgery
2. Check INR 1 day prior to surgery
   If <1.5, proceed with surgery
   If 1.5 to 1.8, consider low-level reversal with Vitamin K
   If >1.8, recommend reversal with Vitamin K (either 1 mg SC or 2.5 mg PO)
3. Recheck INR day of surgery
4. Restart maintenance dose of warfarin the evening of surgery
5. Daily INR until in therapeutic range (>1.9)

Instructions regarding IV UFH use
1. Should start at least 2 days prior to surgery at therapeutic dose using a validated, aPTT-adjusted, weight-based nomogram (ie, 80 U/kg bolus dose IV followed by a maintenance dose of 18 U/kg/h IV)
2. Discontinue 6 hours prior to surgery
3. Restart no less than 12 hours postoperatively at the previous maintenance dose once hemostasis is achieved
4. Discontinue IV UFH when INR is in therapeutic range (>1.9)

Instructions regarding LMWH use
1. Should start at least 2 days prior to surgery at BID therapeutic dose (ie, enoxaparin 1 mg/kg SC BID or dalteparin 100 IU/kg SQ BID)
2. Discontinue at least 12 hours prior to surgery (if surgery is in early A.M. consider holding previous evening dose)
3. Restart usual therapeutic dose within 12–24 hours after surgery once hemostasis is achieved
4. Discontinue LMWH when INR in therapeutic range (>1.9)
5. LMWH should be used in patients undergoing spinal or epidural anesthesia using ASRA guidelines[34]

upon the procedural bleeding risk. In addition, bridging algorithms mandate an INR check the day prior to surgery, with reversal of INR using (oral) Vitamin K if it is elevated (usually >1.8). Last, OAC should be resumed at the usual maintenance dose within 24 hours of the procedure, preferably the same evening. Heparin should be reinitiated within 24 hours of the procedure, provided that adequate hemostasis is achieved, and discontinued once the INR is in therapeutic range (>1.9).

LMWH may facilitate outpatient bridging strategies, while clinical data already presented support the use of LMWH as perioperative bridging therapy in patients with MHVs. An adaptation of a published algorithm for dosing and monitoring OAC, UFH, and LMWH during the bridging episode is shown in Table 3.[24]

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What's New for DVT Prophylaxis for the Medically Ill

Walter Ageno, MD, and
Alexander G. G. Turpie, MD

Prevention of venous thromboembolism (VTE) in medical patients has been less extensively studied than in surgical patients, and, until few years ago, a clear indication for prophylaxis only applied to two specific conditions that carry a well-established risk of thrombosis similar to that of surgical patients: myocardial infarction and acute ischemic stroke. However, autopsy studies consistently found that 70 to 80% of all in-hospital deaths related to pulmonary embolism (PE) were not associated with surgical procedures, but actually occurred in medical patients.[1-5] Others have reported that 50 to 70% of symptomatic venous thromboembolic events related to hospitalization occur in medical patients.[6,7] Finally, a recent study reported a more severe presentation and a significantly worse outcome in patients who developed VTE following an acute medical disease than in patients who developed VTE following surgery.[8] In this study, fatal PE, fatal bleeding, and major bleeding were significantly more common in the medical than surgical patients at 3 months follow-up. Thus, VTE is a major threat in medical patients and prevention is an important aspect of their management.

The first studies on prophylaxis in medical patients were conducted with unfractionated heparin (UFH). In this setting, UFH has been found to be effective in low doses, which are administered subcutaneously without laboratory monitoring. Subsequently, a number of mostly small-sized clinical trials were conducted on general medical patients with the low molecular weight heparins (LMWH) enoxaparin, nadroparin, and dalteparin. The results of these studies have been evaluated by Mismetti and colleagues in a meta-analysis,[9] which first of all confirmed that the risk of deep vein thrombosis (DVT) in medical patients is similar to the risk in general surgery and lies between the moderate- and high-risk groups. The use of pharmacologic prophylaxis, either UFH or LMWH, was clearly shown to reduce the risk of DVT by between 50 and 60% and the risk of

Dis Mon 2005;51:194-199
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.015

clinical and fatal PE by about 50% compared to placebo or no treatment. UFH and LMWH appeared to be similar in efficacy but LMWH was safer with an approximately 50% reduction in the risk of major bleeding.

The first large study on the use of pharmacologic prophylaxis in medical patients using appropriate methodology was the MEDENOX study,[10] which clearly demonstrated the effectiveness of prophylaxis with the LMWH enoxaparin given in doses of 40 mg once daily by subcutaneous injection. In this study, two dosages of enoxaparin, 20 and 40 mg, administered for 6 to 14 days were compared to placebo in 1102 bedridden medical patients. In contrast to most of the previous studies, which did not clearly define the patient population or included patients at very different risks for venous thrombosis, this trial included well-defined categories of patients such as patients with congestive heart failure, acute respiratory failure, acute infection without septic shock, acute rheumatic disorders, or inflammatory bowel disease, all disorders which are known to be at a moderate risk for venous thromboembolism. In this study, the occurrence of DVT was systematically evaluated with venography at the end of the treatment. After 14 days, there was a statistically significant reduction in venous thromboembolic events in the group treated with enoxaparin 40 mg as compared to placebo, but there was no reduction with enoxaparin 20 mg. Major bleeding rates and mortality rates were comparable among the three groups. At 110 days follow-up, there was no evidence of rebound in clinically detected thromboembolic events.

More recently, the LMWH dalteparin was assessed in a large randomized, double-blind, controlled trial in the prevention of VTE in some patient populations. In the PREVENT study,[11] 3706 patients randomly received subcutaneous dalteparin 5000 IU once daily or placebo for up to 14 days. In this study, the primary endpoint was the development of symptomatic DVT, fatal or non-fatal PE, sudden death, and asymptomatic proximal DVT detected by means of compression ultrasonography. The patient population was substantially similar to that of the MEDENOX study. In particular, 52% of patients had heart failure and 30% had respiratory failure. A statistically significant 45% relative risk reduction in the primary endpoint was obtained with dalteparin as compared to placebo (2.8 and 5.0%, respectively), with no substantial difference in the rate of major bleeding events (0.5 and 0.2%, respectively).

In the last few years, new antithrombotic agents have been developed to overcome some of heparin and warfarin limitations. Among others, fondaparinux, a synthetic inhibitor of factor Xa, has been shown to be more effective than LMWH in the prevention of VTE in major orthopedic surgery.[12]

TABLE 1. Disease-related incidence of venous thromboembolism without pharmacologic prophylaxis[19]

Congestive heart failure (NYHA III and IV)	14.6%
Congestive heart failure (NYHA III)	12.3%
Congestive heart failure (NYHA IV)	21.7%
Acute respiratory failure	13.1%
Acute infectious disease	15.5%
Respiratory failure and infection	16.5%
Acute rheumatic disorder	20.7%

In the ARTEMIS study,[13] a phase III clinical study conducted in 849 medical patients, defined as patients older than 60 years admitted because of heart failure, acute or chronic respiratory failure, acute infection, or acute inflammatory disease, fondaparinux (2.5 mg daily subcutaneously) significantly reduced the rate of VTE as compared to placebo, without causing any increase in terms of major bleeding. In particular, the composite endpoint of venographically proven DVT and symptomatic DVT and/or PE was reduced from 10.5 to 5.6%. In addition in this study, the reduction in fatal PE with fondaparinux was statistically significant. The rate of major bleeding events was 0.2% in both groups.

As a result of the clinical trial evidence, international guidelines have recommended the use of pharmacologic prophylaxis, either low-dose UFH or LMWH, in patients with acute medical diseases such as heart failure or acute respiratory failure and in patients who are bedridden and have one of the following risk factors: sepsis, active cancer, previous VTE, acute neurologic disease, or inflammatory bowel disease.[14] Despite this evidence, recent practice audits indicate a significant underuse of thromboprophylaxis in medical patients.[15-17] Reasons for such underuse may include, among others, lack of awareness with guidelines, lack of agreement with guidelines, and lack of outcome data.[18] In particular, concern about bleeding risk and the lack of perception that VTE is a "real issue" are likely to be the most important causes of underuse. Factors that increase the risk of bleeding such as impaired renal function, concomitant use of antiplatelet drugs or antiinflammatory drugs, previous or active bleeding, uncontrolled hypertension, or large cerebral ischemic infarctions are common in medical patients. The application of prophylactic strategies to medical patients is also limited by the heterogeneity of the medical conditions. However, the results of the MEDENOX study have shown that the risk of VTE is consistent among different patient groups (Table 1[19]). Moreover, in addition to the underlying disease, the risk of VTE in medical patients is increased by the fact that most such patients

TABLE 2. Prevalence of concomitant risk factors in medical patients[10]

Chronic respiratory failure	53.4%
Age >75 years	50.3%
Chronic heart failure	32.0%
Varicose veins	25.0%
Obesity	20.1%
Cancer	14.3%
History of venous thromboembolism	9.4%
Hormone therapy	2.0%
Two or more risk factors	66.5%

harbor more than one risk factor (Table 2). Such risk factors include prior VTE, venous insufficiency, obesity, deterioration in general condition, and immobilization.[20]

A number of questions remain to be answered. The optimal doses of LMWH has to be defined for each compound. Doses commonly used in surgical patients have been tested, but the results have not been consistent. The results of the MEDENOX study with enoxaparin provided important evidence that prophylactic doses that are effective in surgical patients may not be effective in medical patients. Moreover, the need for adjusting prophylactic doses to body weight should be considered. The prevalence of overweight and obesity in hospitalized, immobilized patients is significant and common prophylactic doses might be inadequate. The optimal duration of treatment is not known. Most studies were conducted over an average 10 days, based on the average in-hospital stay. It is not known how long medical patients are at risk, although it is apparent that the risk is highest during the acute phase of the illness during initial hospitalization. The results of a large international, randomized controlled trial on the optimal duration of VTE prophylaxis in medical patients are expected. Indeed, patients confined to a nursing home or a chronic care facility have also been shown to have at increased risk for VTE[21]; further studies are also required in this setting.

In conclusion, appropriate diffusion of consensus conference recommendations is now necessary to increase the awareness of the risk of VTE also in medical patients. However, since consensus statements alone are insufficient to ensure the routine use of prophylactic strategies in clinical practice, educational programs should be locally developed that are designed to increase the use of prophylaxis in both teaching and nonteaching hospitals.

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Air Travel-Related Venous Thromboembolism

Bo Eklöf, MD, PhD, Dejan Maksimovic, BS, Joseph A. Caprini, MD, and Catherine Glase, BS

Introduction

Air-travel-related venous thromboembolism (ATVT) was first reported by Homans in 1954.[1] There has been increasing worldwide interest in this subject since the tragic death of 28-year-old Emma Christofferson at Heathrow Airport from pulmonary embolism (PE) after a flight from Sydney in September 2000, which led to many lawsuits from victims against airlines in Australia and the UK. Our interest in ATVT started in 1993 at Straub Clinic and Hospital in Honolulu when we realized that several patients were admitted for extensive, symptomatic deep vein thrombosis (DVT) many times complicated by PE after long air flights. We have published 69 cases of ATVT with a special interest in predisposing risk factors that could influence Virchow's well-known triad.[2,3,4] We divided the risk factors into patient-related internal risk factors and cabin-related external risk factors. Patient-related risk factors were older age, previous DVT/PE, chronic heart disease, malignancy, recent lower limb injury or surgery, overweight, estrogen intake, and smoking. We speculated on the role of cabin-related risk factors: immobilization, "coach position," relative hypoxia, low humidity, insufficient fluid intake, and the diuretic effect of alcohol.

How Serious Is This Problem?

At the Third Pacific Vascular Symposium on Venous Disease in Hawaii 1999, Lord from Sydney estimated that 1 passenger of 100,000 would develop symptomatic ATVT,[5] while Scurr and coworkers from London reported findings of one asymptomatic calf DVT in 10 passengers.[6] So, where is the truth? Several articles on the association between recent travel and VTE have been published:

Dis Mon 2005;51:200-207
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.016

Case control studies

First author	Reference	Year	Controls			Type of travel	Risk factor
			Cases	No.	OR		
Ferrari	7	1999	160	160	4.0	Mix	+
Samama	8	2000	494	494	2.4	Mix	+
Kraaijenhagen	9	2000	186	602	0.7	Mix	−
Dimberg	10	2001	30	891	1.1	Air	−
Hosoi	11	2002	101	106	1.3	Mix	−
Arya	12	2002	185	383	1.3	Mix	−
Rosendaal	13	2002	829	829	3.1	Mix	+
ten Wolde	14	2003	477	1470	0.9	Mix	−
Martinelli	15	2003	210	210	2.1	Air	+

Modified from Ansari MT, Man Yung BC, Huang JQ, Eklof B, Karlberg JPE. Traveller's thrombosis: a systematic review. Submitted for publication. OR = Odds Ratio.

These heterogenous case-control studies have drawn contrasting conclusions largely on crude OR estimates. Four studies concluded that travel is a risk factor. Hosoi and coworkers[11] and Arya and coworkers[12] added that travel may act as a risk factor in travelers with preexisting DVT risk factors. Martinelli and coworkers[15] stratified for air travel and thrombophilia, and air travel and oral contraceptive use, and found a risk increase of 16- and 14-fold, respectively.

- Scurr and coworkers[6] published their study which was presented at the meeting in Hawaii 1999 where the group without compression stockings had 10% asymptomatic calf vein DVT. In a comment by Hirsh and O'Donnell, the main criticism was the potential for biased ultrasonographic assessment.
- Belcaro and coworkers[16] published the LONFLIT study where duplex scan was performed on popliteal and femoral veins of both legs before and after >12-hour flights. In LONFLIT 1 no DVTs were recorded in low-risk subjects, while 2.8% developed DVT in high-risk subjects. In LONFLIT 2 studying high-risk subjects, 4.8% without stockings developed DVT compared to only 0.24% in the group with stockings. In LONFLIT 3 they randomized 300 high-risk passengers into three groups where the control group without prophylaxis had 4.8% DVT, the aspirin group had 3% DVT, while the LMWH group had 0 DVT.[17] LONFLIT 4 contains four articles where different brands of stockings were tested with similar results as in LONFLIT 2.[18-21] In the latest LONFLIT study an oral profibrinolytic drug prevented ATVT, while the control group had an incidence of 5.4%.[22]

- Schwarz and coworkers[23] studied 964 long-haul flight passengers and 1213 nontraveling controls and found 2.8 and 1% VTE, respectively, the majority calf DVT.
- The New Zealand study on ATVT in 1000 low-to-moderate-risk air travelers with a mean total duration of 39 hours in the air showed a frequency of 1.0%.[24]
- Parsi and coworkers[25] published an extensive review with 283 references including their own findings of coagulation defects in 72% of patients with ATVT.
- Lapostolle and coworkers[26] published a study from Charles de Gaulle airport in Paris where, over an 86-month period, 56 of 135.3 million passengers had severe pulmonary embolism. The frequency among those who traveled more than 5000 km was 150 times as high as the frequency among those who traveled less than 5000 km. In an editorial Ansell comments that these findings are clearly the tip of the iceberg with respect to the occurrence of ATVT.
- Other manifestations of thrombosis associated with long-haul flights are reported: subclavian vein thrombosis,[27] stroke due to paradoxical cerebral embolism through a patent foramen ovale,[28] cerebral venous thrombosis,[29] and peripheral arterial thrombosis.[30]

WHO Alerted by the Worrying Reports

The World Health Organization (WHO) reacted responsibly and organized a consultation in Geneva March 12 to 13, 2001[31] with the intention to:

- review and synthesize the available scientific information on ATVT;
- define the extent of the problem;
- identify priority areas of research to find possible solutions if a problem exists;
- try to reach a consensus of pragmatic strategies for prevention based on currently available evidence.

Ten experts were invited to present available scientific information, and 15 of the major airlines were represented, none from the USA. The experts agreed:

- that an association probably exists between air travel and venous thrombosis;
- such an association is likely to be small and mainly affects passengers with additional risk factors for venous thromboembolism;
- similar links may exist for other forms of travel;

- the available evidence does not permit an estimation of actual risk, and therefore, public health recommendations cannot be made at the present time.

The representatives of the airlines agreed:

- that an association between venous thrombosis and travel in general probably exists;
- that there are insufficient data on which to make recommendations;
- consequently, the airlines and IATA are committed to support further research.

It was the unanimous view of the participants that these studies should be undertaken as soon as possible under the auspices of WHO and supported by an independent scientific committee in close collaboration with IATA and ICAO. The priorities for research were suggested in three areas and protocols for funding were drawn up:

- A set of multicenter, international, epidemiological studies including a large prospective cohort study examining hard clinical endpoints to answer the questions: is there an association and, if so, what is the absolute risk? What is the size of the problem? Studies on aircrew and cabin staff, as well as populations from multinational companies, are also planned. Principle investigator is Frits Rosendaal from The Netherlands.
- A set of special small-scale studies seeking intermediate endpoints and/or specific questions in groups of volunteers examining isolated independent environmental and behavioral risk factors. These studies will include physiopathological studies using hypobaric chambers. The principle investigator is William Toff from UK.
- A set of interventional studies to assess preventive measures on the occurrence of ATVT with standardized diagnostic methods, involving passengers in experimental well-controlled studies. Four sites are chosen for this study: Chicago (PI Joe Caprini), Honolulu (PI Bo Eklof), London (PI John Scurr), and Vienna (PI Hugo Partsch).

Evanston Northwestern Healthcare Travel Survey

Patients and Methods

More than 20,000 risk assessment questionnaires were distributed in various hospital-associated circulars. Travelers were asked to fill in demographic data such as age, sex, height, and weight and to indicate the number of 8-hour flights, road trips, or train rides within the past year.

TABLE 1. Risk factor scores and results

Number of Risk Factors*	Number of Responses	Average Age (years)**	Average BMI**	Long-Distance Travel <1 year Ago
0	4 (0.5%)	32.0	21.72	2 (50.0%)
1	59 (7.7%)	69.9	22.05	30 (50.8%)
2	179 (23.2%)	68.3	24.80	111 (62.0%)
3	205 (26.6%)	70.5	25.22	125 (61.0%)
4	171 (22.2%)	70.9	26.06	110 (64.3%)
5+	153 (19.8%)	72.3	27.25	82 (53.6%)
Total	771	70.2	25.45	460 (59.7%)
M	197	72.8	26.18	122 (26.5%)
F	574	69.3	25.20	338 (73.5%)

*Risk factor is defined here as a "Yes" response to any question on the brochure, age over 40, or a BMI greater than 25.
**Both of these categories were included in the calculation of the risk factor scores.

The remainder of the questionnaire had travelers respond to questions involving their history of blood clots, recent immobilization, surgical history, and remark on any diseases related to hypercoagulability (heart attack, stroke, cancer, etc.). Finally, women were asked to indicate if they were recently pregnant, taking oral contraceptives, or receiving hormones. Based on the number of risk factors for VTE present, the individuals were categorized as being low, moderate, high, or highest risk according to ACCP guidelines. An electronic version of the questionnaire was also available on the hospital web site. To date, 827 brochures have been received, including 771 fully completed responses (Table 1).

Results

Results from the initial group of brochure respondents show that an overwhelming majority of people had a number of risks associated with developing a VTE. A total of 19.8% of subjects had five or more VTE risk factors. The average number of risk factors was greater in women due to hormone replacement therapy (HRT) and pregnancy/postpartum. Although no women in this initial group were pregnant or postpartum, 197 were taking HRT. Study participants with four risk factors had the highest percentage of long-distance travel within the past year (64.3%). Finally, 10.8 and 11.9% of the traveling participants had a previous VTE or had a family history of blood clots, respectively (Table 2).

Current Advice for Prevention of ATVT

The suggested research projects will hopefully answer the questions that were raised within the next few years. While waiting for the outcome of the research, what can we recommend to the 1.5 billion people who fly

TABLE 2. Associated risk factors of thrombosis in travelers

	Prior Clot	Family History Clot	Swollen Legs	Varicose Veins	Ileitis or Colitis
M	29 (14.7%)	12 (6.1%)	65 (33.0%)	43 (21.8%)	11 (5.6%)
F	54 (9.4%)	80 (13.9%)	247 (43.0%)	289 (50.3%)	41 (7.1%)
Total	83 (10.8%)	92 (11.9%)	312 (40.5%)	332 (43.1%)	52 (6.7%)

Breathing Problems	3 days Bed Rest	Pelvic/Leg Fractures	MI/Stroke	Major Surgery	Cancer	HRT
14 (7.1%)	7 (3.6%)	0 (0%)	37 (18.8%)	11 (5.6%)	44 (22.3%)	—
39 (6.8%)	24 (4.2%)	4 (0.7%)	38 (6.6%)	16 (2.8%)	149 (26.0%)	197 (34.3%)
53 (6.9%)	31 (4.0%)	4 (0.5%)	75 (9.7%)	27 (3.5%)	193 (25.0%)	197 (25.6%)

every year? The cabin-related risk factors that may lead to hypercoagulation and stasis can be remedied by simple means:

- drink plenty of nonalcoholic fluids to avoid dehydration;
- move the feet and legs and take deep breaths in the seat several times every hour to avoid pooling of blood in the legs.

Passenger-related risk factors that can trigger any of the factors in Virchow's triad may be potentiated by the cabin-related risk factors and put these passengers at higher risk to develop DVT. The awareness of this problem has to be increased among the public as well as among the physicians:

- all passengers with a tendency for significant swelling of the lower legs, and all passengers with risk factors for DVT, will most probably benefit by wearing graduated compression stockings during the flight;
- passengers with severe risk factors such as previous DVT or pulmonary embolism, congenital or acquired hypercoagulability, recent surgery, malignancy, or obesity will need further prevention and should discuss with their physician whether prophylaxis with low molecular weight heparin should be given during the flight.

It should be easy to advise passengers with multiple risk factors. The main problems are with young passengers like Emma Christofferson with unknown internal risk factors such as a positive-factor V Leiden or taking contraceptive pills, upon which the cabin-related risk factors are added during a long flight. There is a need for more information for the public, the airlines, and the physicians to increase the awareness of ATVT. WHO has so far only partially funded the first two projects. We hope that full funding will be available so that the important research projects can be

completed and the facts disseminated about the true risks and ways to prevent ATVT. For further information visit www.pacificvascular.org and link to 2002 Symposium-Air travel-related venous thromboembolism.

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Oral Anticoagulants—The Old and the New

Jack Ansell, MD

Introduction

Unfractionated heparin (UFH) and the vitamin K antagonists (VKAs) are highly effective in the prevention and treatment of venous thromboembolism (VTE), but they possess inherent drawbacks that limit their usefulness and effectiveness.[1] The vitamin K antagonists (VKA) suffer from a slow onset and offset of action, an unpredictable response, and multiple food and drug interactions and require intensive monitoring. As a consequence, there is global under-use and poor management of the VKAs resulting in a high rate of adverse events.[2,3] Unfractionated heparin must be given intravenously (usually by continuous infusion), requires monitoring, and can cause heparin-induced thrombocytopenia (HIT) and thrombosis.[4] Low molecular weight heparin (LMWH), although having improved attributes, must still be given by subcutaneous injection and still has the potential to produce HIT. To counter these limitations, many new anticoagulants under development are easier to administer (oral), have a predictable dose response, do not require monitoring, do not interact with foods or drugs, and can be used for both acute and chronic indications.[5] The most advanced agents in development are specific, direct, oral factor Xa or IIa inhibitors.

Factor Xa Inhibitors

Fondaparinux and idraparinux are two synthetically derived molecules based on the pentasaccharide found in UFH necessary for antithrombin binding.[6] Both are specific, indirect inhibitors of activated factor Xa via their binding and activation of antithrombin, and neither have an effect on thrombin. Both are administered subcutaneously; fondaparinux having a 17-hour half-life is given once daily, and idraparinux, having a 3- to 4-day half-life, is given once weekly. They require no coagulation monitoring, do not cause heparin-induced thrombocytopenia, and are cleared by the kidney. Fondaparinux has been studied in over 7000 patients undergoing

Dis Mon 2005;51:208-212
0011-5029/2005 $30.00 + 0
doi:10.1016/j.disamonth.2005.03.017

hip and knee replacement or hip fracture surgery[7] producing an approximate 50% relative risk reduction in VTE compared to LMWH. It has also been shown to be effective for the initial, acute treatment of deep venous thrombosis (DVT) or pulmonary embolism (PE) compared to LMWH or UFH, respectively,[8,9] and is now approved for both conditions. Fondaparinux is targeted for short-term treatment, while idraparinux may be competitive with oral anticoagulants because of its long half-life. Phase III clinical trials for the long-term treatment of DVT and PE have recently been completed and results are pending. A long-term stroke prevention in atrial fibrillation trial is also currently ongoing.

A number of small-molecule *direct* inhibitors of factor Xa are also in development. These agents are available orally, appear to have linear and predictable pharmacokinetics, and may not require coagulation monitoring. They are dosed once or twice daily. Razaxaban has undergone Phase II testing for the prevention of VTE in knee replacement surgery.[10] At the lowest dose, razaxaban was associated with an 8% rate of venogram-documented VTE compared to a 16% rate for enoxaparin, with no significant increase in major bleeding. Higher doses produced increased efficacy, but with more bleeding. Phase III trials are now in progress. A number of other oral Xa inhibitors are entering Phase II to III clinical trials.

Factor IIa or Thrombin Inhibitors

Parenteral direct thrombin inhibitors (DTIs) are currently available for limited indications,[11] but oral DTIs are poised to compete with the VKAs. Ximelagatran is an oral DTI furthest along in development. It is a prodrug of the active anticoagulant melagatran, is rapidly absorbed after an oral dose, is promptly metabolized to melagatran, has a half-life of approximately 4 to 5 hours, and achieves effective anticoagulant levels for up to 12 hours so that twice daily dosing is effective.[12] Ximelagatran is not metabolized by the hepatic CYP450 enzymes and has minimal if any drug–drug interactions. It is cleared by the kidney.

In orthopedic surgery, ximelagatran has been shown to be as effective as a LMWH or VKA comparator to prevent postoperative VTE.[13] In a randomized, double-blind trial of the treatment of acute DVT,[14] ximelagatran, given for 6 months, was as effective and safe as enoxaparin followed by warfarin for 6 months in 2500 patients (2.1% versus 2.0% recurrence, respectively; 95%CI, −1.0 to 1.3%) with no difference in major bleeding (1.3% versus 2.2%, respectively) (Table 1). In an extended VTE prophylaxis trial after 6 months of standard treatment for acute DVT, 1200 patients received ximelagatran, 24 mg twice daily, or

TABLE 1. Efficacy and safety results of four major ximelagatran trials

	Thromboembolism		Major Bleeding		ALT Elevation	
	Comparator	**Ximelagatran**	**Comparator (%)**	**Ximelagatran (%)**	**Comparator (%)**	**Ximelagatran (%)**
Acute and chronic treatment of DVT	Enoxaparin-warfarin	Ximelag 36 mg bid				
THRIVE Treatment study	2%	2.1%	2.2	1.3	2.0	9.6
Extended treatment of DVT	Placebo	Ximelag 24 mg bid				
THRIVE III Study	12.6%	2.8%	1.3	1.1	1.2	6.4
Atrial fibrillation	Warfarin INR 2-3	Ximelag 36 mg bid				
SPORTIF III	2.3%	1.6%	1.8	1.3	1	6.0
SPORTIF V	Warfarin INR 2-3	Xi melag 36 mg bid				
	1.2%	1.6%	3.1	2.4	0.8	6.0

ALT = alanine aminotransferase >3 times upper limit of normal.
In each study, the ALT was significantly elevated compared to the comparator.
There was no significant difference in major bleeding in any of the individual studies.
In the THRIVE Treatment studies and the SPORTIF studies, ximelagatran was noninferior to the comparator.
In the THRIVE III studies, ximelagatran was significantly superior to placebo.

placebo, and then were followed for an additional 18 months (Table 1).[15] The cumulative incidence of recurrent VTE in the placebo arm was 12.6% versus 2.8% in the ximelagatran arm (95%CI, 0.09 to 0.30%, $P < 0.0001$) with no difference in major bleeding.

Ximelagatran was compared to warfarin in over 7000 patients with nonvalvular atrial fibrillation for the prevention of stroke or systemic embolism in two trials (Table 1).[16] Combined results found that 2.5% of patients in each group experienced a primary outcome event with an annualized rates of 1.6% versus 2.3% in SPORTIF III and 1.6% versus 1.2% in SPORTIF V for ximelagatran versus warfarin, respectively (RRR of 1% and ARR of 0.1%, $P = 0.92$). The pooled rate of major bleeding showed a significant decrease favoring ximelagatran (RRR 26% and ARR 0.8%, $P = 0.03$).

Last, in a Phase II dose-ranging study, ximelagatran + aspirin in patients with an acute coronary syndrome resulted in a significantly reduced rate of the combined endpoint (death, nonfatal MI, or serious recurrent ischemia) compared to aspirin alone (12.7% versus 16.3%, $P = 0.0357$).[17]

In all long-term studies, ximelagatran was associated with a 6 to 12% increase in alanine aminotransferase >3 times the upper limit of normal in the first 2 to 6 months of therapy. Values generally returned to normal whether drug was continued or stopped.

Dabigatran etexilate,[18] another DTI, has recently completed a Phase II dose escalation study of both once- and twice-daily dosing schedules in patients undergoing total hip replacement. The results of this trial are not yet available.

Conclusion

The treatment of thromboembolic disease is about to undergo a major change. For the first time, new oral anticoagulants may be available that require no coagulation monitoring or dose adjustment, and they have metabolic pathways that reduce or eliminate the problem of drug or food interactions. Because of their rapid onset of action, these agents may be suitable alternatives to heparin and the various heparin analogues as well as warfarin. As a result, few patients in the future may need hospitalization for the treatment of VTE, and acute and chronic therapy will merge into one therapeutic continuum with the same agent. With greater ease of therapy and possibly greater safety, physicians may be more willing to employ therapy for conditions such as atrial fibrillation and more likely to use prolonged extended therapy for patients with VTE.

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