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Clinical Cornerstone

Prevention of Thromboembolic Events

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Clinical Cornerstone

PREVENTION OF THROMBOEMBOLIC EVENTS

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Clinical Cornerstone

PREVENTION OF THROMBOEMBOLIC EVENTS

Contents

Introduction

Venous thromboembolism (VTE) and its manifestations—including deep vein thrombosis (DVT) and pulmonary embolism (PE)—are serious medical conditions associated with high rates of morbidity and mortality.[1] An estimated 300,000 patients are hospitalized each year in the United States due to VTE.[2] Furthermore, patients hospitalized for reasons other than VTE typically have at least 1 risk factor for VTE.[3] Depending on the surgical procedure, DVT occurs in 10% to 60% of hospitalized patients who do not receive prophylaxis. Studies have found that 10% of hospital deaths are attributed to PE, with the majority of these deaths occurring in patients who have not recently undergone surgery.[3] The incidence of VTE also is associated with enormous financial cost; an estimated $1.5 billion is spent each year on expenses associated with DVT in the United States alone.[4]

VTE is a life-threatening illness that has multiple causes but few warning signs. Symptoms of DVT may include pain, erythema, tenderness, and swelling of the affected limb, whereas PE often presents as sudden breathlessness with chest pain or collapse with shock in the absence of other causes.[5] Yet, VTE prophylaxis is often underutilized. This issue of *Clinical Cornerstone* presents 6 articles that focus on the need for greater awareness of VTE and encourage health care professionals to take appropriate preventive measures to reduce the incidence of VTE and its potentially life-threatening manifestations.

The first article by Franklin Michota, MD, describes the epidemiology of VTE, its consequences, and how to identify patients at risk for VTE. Dr. Michota also highlights the need for prompt and accurate recognition of risk factors that can lead to the implementation of effective VTE prophylaxis.

The second article by Walter Ageno, MD, and Alexander G.G. Turpie, MD, reviews the findings of several studies that investigated the use and effectiveness of thromboprophylaxis among medical patients. They found that these studies support the evidence-based recommendations for the systematic use of pharmacologic agents for VTE prevention in patients at risk for VTE.

The third article by Arthur Wheeler, MD, takes a close look at the updated guidelines for the prevention of VTE established by the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy and discusses the high prevalence of VTE among medically ill patients. Dr. Wheeler also describes various strategies that can be used for VTE prophylaxis, highlighting relevant clinical studies that support the use of antithrombotic therapy.

Practical applications of the ACCP revised guidelines on VTE prevention for primary care physicians is the focus of the fourth article by Geno J. Merli, MD, FACP. Physicians are encouraged to assess VTE risk factors for each patient—as well as the underlying illness or surgical procedure of each patient and the benefits and risks of possible therapies—to determine the appropriate course of action for each patient. This article also discusses the need for hospitals to adopt clinical guidelines for VTE prevention, recognizing the growing impact of an aging population that experiences more surgical procedures with shorter durations of hospital stays.

The fifth article by Alex C. Spyropoulos, MD, FACP, FCCP, reports on the findings of several studies regarding pharmacologic therapy options for thrombosis management in VTE and non–ST-elevation acute coronary syndrome. Dr. Spyropoulos discusses various efficacy, safety, and pharmacoeconomic considerations relating to the selection of a low-molecular-weight heparin versus unfractionated heparin for the prevention of VTE events.

The sixth article by Geno J. Merli, MD, FACP, describes specific strategies that can be used to prevent VTE, including anticoagulant therapy with heparin (low-molecular-weight heparin or unfractionated heparin), direct thrombin inhibitors, oral anticoagulants (such as warfarin), and mechanical methods. Dr. Merli also discusses the role of aspirin therapy in patients at risk for VTE.

Greater awareness of VTE and the need for VTE prophylaxis can lead to widespread use of effective interventions to help reduce the incidence of thromboembolic events in patients who receive health care services throughout the United States.

Geno J. Merli, MD, FACP, and
Deepak L. Bhatt, MD, FACC, FSCAI, FESC
Guest Editors

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Venous Thromboembolism: Epidemiology, Characteristics, and Consequences

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Venous thromboembolism (VTE) and its manifestations, including deep vein thrombosis (DVT) and pulmonary embolism (PE), pose a life-threatening health problem for thousands of people each year. The diagnosis of VTE is frequently missed, however, because few signs and symptoms are recognized. Symptoms of DVT may include pain, erythema, tenderness, and swelling of the affected limb, whereas PE often presents as sudden breathlessness with chest pain, or collapse with shock in the absence of other causes. Greater awareness of the epidemiology of VTE, the consequences of VTE, and the risk factors for VTE can help health care providers take appropriate preventive measures to reduce the incidence of VTE. (*Clinical Cornerstone.* 2005;7[4]:8–15)

Venous thromboembolism (VTE) is a silent, preventable killer. VTE encompasses several manifestations of the same disease process, including deep vein thrombosis (DVT) and pulmonary embolism (PE). In VTE, abnormalities in blood flow, the blood vessel wall, or blood clotting components contribute to formation of a thrombus.[1] DVT refers to a thrombus in the deep veins, most often in the lower extremities. The thrombus can embolize and become lodged in the pulmonary arteries, resulting in PE, which frequently occurs without warning and is often fatal.

Despite recent consensus guidelines on the prevention of VTE[2] and the availability of antithrombotic agents such as the low-molecular-weight heparins, incidence of VTE and its associated manifestations remains high.[3,4] Incidence of VTE is 10% to 40% in general medical and surgical patients and 40% to 60% in orthopedic surgery patients.[2] In the United States, PE accounts for more than 250,000 hospitalizations annually.[4] Although the risks of VTE are well recognized in orthopedic and surgical patients, the majority of all in-hospital deaths due to PE are in nonsurgical patients[5,6]; however, most medical patients do not receive any form of VTE prophylaxis.[7]

Recent articles have highlighted the need for greater awareness of VTE and its manifestations.[8–10] Because there are few signs and symptoms of VTE, the diagnosis of DVT or PE is frequently missed.[11] In one study of 2388 autopsies in a general hospital population, PE accounted for 10% of all in-hospital deaths. Of these patients, 83% had DVT in the legs at autopsy, including only 19% who had symptoms of DVT before death.[12] Symptoms of DVT can include pain, erythema, tenderness, and swelling of the affected limb.[1] PE often presents as sudden breathlessness with chest pain, or collapse with shock in the absence of other causes.[1] A thorough understanding of VTE, awareness of the signs and symptoms, and recognition of factors that place a patient at risk will help physicians take appropriate preventive measures to reduce the incidence of VTE and its potentially life-threatening manifestations.

EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

Of all patients with VTE, about two thirds have DVT alone, whereas one third also have PE.[13,14] The annual incidence of diagnosed, objectively confirmed VTE in

the general population is about 1 to 2 per 1000 people, with ~66% of cases being first episodes.[11] The annual incidence of PE is slightly under 1 per 1000 people.[15] Postthrombotic syndrome (PTS) occurs in one third of patients after a symptomatic episode of DVT.[1,16]

KEY POINT

The annual incidence of diagnosed, objectively confirmed VTE in the general population is about 1 to 2 per 1000 people.

About 37% of all cases of VTE occur in patients who are either hospitalized or recently placed in a nursing home.[17] A study of 51,645 hospitalized patients over a 21-month period showed the prevalence of acute diagnosed PE to be 1% (526 of 51,645).[18] PE was observed at autopsy in 15% (59 of 404) of all patients on whom autopsies were performed.[18] Among those patients with PE at autopsy, PE contributed to death in 22 (37%) of 59 patients. Among those patients who died from PE, the diagnosis was unsuspected in 14 (70%) of 20 patients.[18] About 75% of all in-hospital deaths from PE occur in nonsurgical patients.[5]

KEY POINT

About 75% of all in-hospital deaths from PE occur in nonsurgical patients.

VTE is uncommon in patients younger than 20 years; most children diagnosed with VTE have a serious underlying primary illness, such as cancer, chronic total parenteral nutrition dependency, or congenital heart disease.[19] The incidence of VTE increases with increasing age, doubling with each decade after age 40 years.[11,17] In addition, PE accounts for a higher proportion of diagnosed episodes of VTE as age advances.[11,17] In a study of 342,000 inhabitants of Western France, the annual incidence of VTE reached 1 per 100 for individuals over the age of 75 years.[17] In this same study, 63% of patients were at home when VTE occurred; however, 16% had been hospitalized within the previous 3 months. Approximately two thirds of these patients had been in a medical unit, and one third had been in a surgical unit.

Autopsy studies show that PE may cause or contribute to a high percentage (0.2%–20.3%) of deaths in hospitalized medical and surgical patients.[12,18,20–22] In a retrospective analysis of 391 surgical patients in Malmo, Sweden, from 1951 to 1988 in whom PE was found at autopsy, PE was considered to be the cause of death in 113 (29%) patients, a contributor to death in 104 (27%) patients, and incidental in 174 (45%) patients.[20] In another study of 4881 general surgical patients in a Denmark hospital, fatal postoperative PE was found in 9% of patients who had an autopsy performed.[21] The incidence of fatal postoperative PE among patients who received prophylaxis was 3.5% compared with 11.2% in patients who did not receive prophylaxis.[21]

KEY POINT

The incidence of VTE increases with increasing age, doubling with each decade after age 40 years.

A retrospective analysis of 2427 autopsies from 1985 through 1989 confirmed PE as the cause of death in 92 (3.8%) patients, with no difference in incidence between medical and surgical patients.[22] In this study, classic symptoms of PE were often absent in patients before death, with dyspnea present in 59% of patients, chest pain in 17% of patients, and hemoptysis in 3% of patients. Only 32% of patients had PE correctly assigned as the cause of death on the death certificate.

In a 5-year retrospective study of all autopsy reports in a general hospital patient population, PE was thought to be the cause of death in 239 (10%) of 2388 patients, with 15% of patients <60 years of age and 83% having DVT in the legs. Only 19% of patients had symptoms of DVT before death, and only 3% had undergone investigation for DVT, again illustrating the silent nature of this condition in many patients.[12]

CONSEQUENCES OF VENOUS THROMBOEMBOLISM

VTE is a common hospital-associated complication, with 10% of hospital deaths attributed to PE.[12] Death due to

PE is frequently the first sign of VTE and often occurs suddenly, before effective intervention can be provided. In a prospective registry of 5451 patients with ultrasound-confirmed DVT in the United States, concomitant PE was identified in 793 (14.5%) of patients.[23] PE accounts for 60,000 to 100,000 deaths in the United States annually.[23,24] Although generally uncommon in younger people and children, VTE is becoming recognized as a significant cause of morbidity and mortality in children.[19]

KEY POINT

VTE is a common hospital-associated complication, with 10% of hospital deaths attributed to PE.

VTE results in serious long-term as well as short-term complications, which can significantly affect a patient's quality of life (QOL).[9,25] Long-term recurrent VTE can result in thromboembolic pulmonary hypertension and damage to the venous valves, as well as PTS.[24] PTS can be extremely debilitating and is characterized by chronic leg symptoms, including persistent pain, swelling, cramping, skin discoloration, necrosis, and ulceration of the affected limb due to venous hypertension.[24] In extreme cases of PTS, amputation of the limb may be necessary.[9] In a study of 528 patients with a first episode of symptomatic DVT, the cumulative incidence of recurrent VTE after 2, 5, and 8 years was 17%, 24%, and 30%, respectively.[26] In the same study, the cumulative incidence of PTS after 2, 5, and 8 years was 25%, 30%, and 30%, respectively. Survival after 8 years was 69%.

A health-related QOL study of 359 patients after DVT diagnosis showed that, on average, QOL improved during the 4 months following diagnosis.[25] Mean scores on all physical and mental health surveys and disease-specific symptom questionnaires improved significantly ($P < 0.001$) during the 4-month period. However, QOL deteriorated in about one third of patients, with a worsening PTS score associated with worsening QOL.[25] In another QOL study,[27] 45 patients with VTE scored significantly lower on all subscales of a questionnaire compared with the norms associated with the general US population ($P < 0.05$). Patients with PTS also had more impairment of QOL than patients without PTS. In addition to affecting an individual's QOL, the direct and indirect medical costs associated with VTE are a burden to patients and society.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

The high prevalence, silent nature, significant financial and personal burden, and potentially rapid mortality of VTE all underscore the importance of recognizing the risk factors and initiating appropriate prophylactic measures. Early identification of patients at risk for VTE and its manifestations should substantially reduce morbidity and mortality from this disease.

As shown in the **table**, risk factors for VTE have been identified, including age >40 years, immobilization or conditions resulting in venous stasis, conditions resulting in vessel wall damage, abnormalities in circulating coagulation elements, and previous DVT or PE.[2,11,24] Risk factors tend to be cumulative, so that older individuals are more likely than younger individuals to have other factors, such as immobility, malignancy, obesity, or other

TABLE. RISK FACTORS FOR VENOUS THROMBOEMBOLISM (VTE).[2]

Surgery
Trauma (major or lower extremity)
Immobility, paresis
Malignancy
Cancer therapy (hormonal, chemotherapy, or radiotherapy)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraception or hormone replacement therapy
Selective estrogen receptor modulators
Acute medical illness
Heart or respiratory failure
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Smoking
Varicose veins
Central venous catheterization
Inherited or acquired thrombophilia

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diseases, that increase the risk of VTE.[2] Although patients at high risk for VTE can be identified, it is not possible to predict which patients will develop VTE.[2] Even patients at low risk for VTE can develop a sudden, unexpected VTE event.

One approach to identifying risk and prophylaxis for VTE considers both an individual's predisposing factors for VTE, as well as risks associated with current illnesses or medical/surgical procedures.[2] An example is stratification of risk for surgical patients into categories of low, moderate, high, and highest risk based on age, presence of additional risk factors, and type of surgery, with prophylaxis based on an individual's determined level of risk.[28] An alternative approach involves assuming similar risk for specific groups of patients categorized by disorder or type of hospital service and routinely implementing standard prophylactic measures.[2] For example, specific prophylactic recommendations have been tailored for patients undergoing different types of surgeries, for trauma patients, for patients with specific medical conditions, for cancer patients, for patients in critical care, and for individuals traveling long distances.[2]

Whatever method is used, efforts to identify patients at risk for VTE aids initiation of appropriate prophylactic measures and reduces rates of DVT and PE. In a study of hospitalized patients at risk for DVT, a computer program was developed based on an 8-factor risk assessment strategy to identify patients at risk for DVT and PE.[8] The major risk factors of cancer, prior VTE, and hypercoagulability were assigned a score of 3; the intermediate risk factor of major surgery was assigned a score of 2; and the minor risk factors of advanced age, obesity, bed rest, and the use of hormone replacement therapy or oral contraceptives were assigned a score of 1. An increased risk of VTE was defined as a cumulative risk score of at least 4. Using this risk stratification system, physicians in the computer-alert program increased the use of prophylaxis for at-risk patients, resulting in an 8.2% reduction in the rate of DVT or PE within 90 days compared with rates in at-risk patients whose physicians were not alerted.

As more patients are discharged from the hospital sooner after orthopedic and all types of surgeries, risk of VTE in the outpatient population will also increase. Therefore, each patient should be screened for risk of VTE prior to or at the time of hospitalization so appropriate prophylaxis can be provided. In addition, knowledge of a patient's risk factors for VTE will influence interpretation of objectives measures, such as D-dimer, venous ultrasonography, and ventilation-perfusion scanning.

KEY POINT

Efforts to identify patients at risk for VTE aids initiation of appropriate prophylactic measures and reduces rates of DVT and PE.

CONCLUSIONS

VTE and its manifestations, including DVT and PE, are preventable. Yet because there are few signs and symptoms, VTE often goes unrecognized; therefore, a greater awareness of VTE and its risk factors is needed. Given the high incidence of VTE, DVT, and potentially life-threatening PE, prompt and accurate recognition of risk factors is crucial to implementing effective prophylaxis and reducing the burden of VTE and its manifestations.

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Dialogue Box

EDITORIAL BOARD

Given the relatively high prevalence of venous thromboembolism (VTE) in hospitalized patients, has any thought been given to just screening patients with venous duplex scans?

MICHOTA

This strategy has been investigated and found to be inadequate. Duplex scanning, even with high operator skill, only has an 80% sensitivity for asymptomatic deep vein thromboembolism (DVT). This would fail to detect too large a number to be a reliable strategy, not to mention the cost and the technical issues of trying to do this on a regular basis. Ultimately, required technology for such a strategy may be developed, but we don't have it now. Ideally, we would have some serologic marker of thrombogenicity that could be measured in everybody so that when you fell into the thrombogenic range, you'd get prophylaxis.

EDITORIAL BOARD

Why is DVT prophylaxis not as effective as one might think?

MICHOTA

First let me say that we do have over 30 years of randomized clinical trial evidence that DVT prophylaxis reduces thromboembolic morbidity and mortality. However, variability exists in individual patients in terms of how they respond to our current prophylactic measures. Although we clearly have effective pharmacologic prophylactic measures, there are some patients whose thrombogenicity is high enough that they may be more resistant to even our most intense pharmacologic strategy. Today, our biggest problem lies in the fact that many patients at risk for DVT still don't get any prophylaxis at all. In the DVT-FREE registry, less than half of patients who were hospitalized and developed a symptomatic event received any form of prophylaxis. So regardless of the risk reduction possible for any given prophylaxis strategy, if we don't use it, there is no chance for it to be effective.

EDITORIAL BOARD

Since prophylactic measures would not be effective in patients with established DVT, is it possible that some of the failures seen with prophylactic therapy in clinical trials were due to asymptomatic VTE being already present at the time of entry into the study?

MICHOTA

No, that was generally controlled for. In fact, some studies actually used venograms or other sensitive modalities to exclude DVT in patients prior to enrolling them into study populations.

EDITORIAL BOARD

Is immobility the primary cause for the increased thrombogenicity we see in hospitalized patients, or do you think something else is going on?

MICHOTA

Other factors have to be involved, particularly in the medically ill population. To support this, one needs to look no further than the situation seen in patients with Lou Gehrig disease (ie, amyotrophic lateral sclerosis). Have you ever seen or heard a case report of somebody with amyotrophic lateral sclerosis dying of pulmonary embolism (PE)? You'd scour the literature and discover there's no association between Lou Gehrig disease and PE.

EDITORIAL BOARD

And they have no muscle tone.

MICHOTA

The way I've looked at this is that ambulation is probably a marker of health, and thus I'm not so certain that walking prevents DVT any more than that the state of immobility is clearly a causative factor in and of itself. It seems more likely that the ability to walk is just a marker of somebody whose thrombogenicity is low, which is closer to what we would expect in the community population; there is an 8-fold lower incidence of VTE in

Dialogue Box

the community than in a hospitalized population. Thus, when you look at a nursing home population that's chronically immobile or bed-bound, their actual thrombogenicity may be low, provided nothing acute is going on. If that same patient develops a urinary tract infection, becomes confused, and perhaps less mobile (requiring more assistance to get out of bed and so forth), that is when their thrombogenicity goes up—not because they can't get out of bed anymore, but because of their acute systemic illness. Certainly, we know that ambulation can improve venous flow and decrease stasis and so forth. But that may not be where the action is. The action may be in the thrombogenic state from whatever made them unable to walk anymore.

EDITORIAL BOARD
Please comment on the future biochemical markers for looking at thrombogenicity.

MICHOTA
Well, at this point, that's the holy grail. Although everybody is looking for markers that would allow us to quantitatively measure dysregulation of the coagulation system and thus increased thrombogenicity, at the moment, there isn't any. We don't even have one on the drawing board.

EDITORIAL BOARD
Any role for D-dimers?

MICHOTA
They have no role for "ruling-in" a diagnosis of DVT or PE in any patient population. D-dimers do have a role in excluding VTE in an outpatient or emergency room population. Enzyme-linked immunosorbent assay (ELISA)–based assays are required, and in a patient with low or moderate clinical suspicion, a negative D-dimer can rule out DVT. However, once a patient is admitted to the hospital, virtually all patients will have some elevation of D-dimer in that setting. Thus, the specificity drops so low that the negative predictive value, even if they're ELISA-based assays, are too low to be clinically useful.

EDITORIAL BOARD
In what patients would you launch a workup for an underlying thrombophilia?

MICHOTA
The patient with idiopathic DVT. This would generally be someone less than 45 years of age or someone more than 45 years of age who has no identifiable risk factors for clotting. We would also look for a thrombophilia in a patient who had what we consider to be minor risk factors but yet had a surprisingly high clot burden (meaning their whole leg was packed with clot from the ankle to the thigh), as well as the patient with a clot in a very atypical location, such as the upper extremity without a cervical rib issue or a central catheter access.

EDITORIAL BOARD
What would be your workup?

MICHOTA
Let me begin by saying we categorically treat people for 6 months before beginning a workup. Although you can do some genetic testing, such as Factor V Leiden mutation and prothrombin gene mutation, even if a patient is on anticoagulation therapy, unless there is some compelling reason to know their genetic status (such as to counsel a sibling who smokes or who is on the birth control pill), we generally wait at least 6 months. At that point, we counsel the patient as to what we are going to do if we find an abnormal result. For example, if we find a positive result, would the patient be willing to receive anticoagulation drugs for extended periods of time? If not, we may not even test this patient. Since there is no certainty of the absolute implications in any given individual, the likelihood is that, erring on the side of caution, we would recommend extended anticoagulation for patients we know have positive results; if the latter would not be an option, we may simply not want to even know the result.

In direct response to your question, our initial battery of tests would check for the prothrombin gene mutations, Factor V Leiden mutation, and homocysteine since

Dialogue Box

they are the most common thrombophilic abnormalities. If these tests came back negative, we would then look for protein C and S deficiencies, antithrombin-III deficiency, and anticardiolipin and antiphospholipid antibodies. It's important to recognize that you should never test for the factor deficiencies within 4 weeks of an acute clot because your results will be difficult to interpret and may lead to a false-positive result. Such patients do not have thrombophilia; they've just had consumption of these factors because of the acute clot.

Clinical Trials of Deep Vein Thrombosis Prophylaxis in Medical Patients

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Autopsies and clinical studies have shown that venous thromboembolism (VTE) is a common cause of morbidity and mortality in medical patients. Prophylaxis of VTE has been less extensively studied in medical patients than in surgical patients, and the results of recent practice audits indicate that the use of thromboprophylaxis is uncommon in medical patients. In the past few years, 3 large randomized clinical trials have demonstrated the efficacy and safety of prophylaxis of VTE in the medical setting. The prophylaxis in MEDical patients with ENOXaparin (MEDENOX), Prospective Evaluation of Dalteparin Efficacy for PREVENTion of VTE in Immobilized Patients Trial (PREVENT), and ARixta for ThromboEmbolism Prevention in a Medical Indications Study (ARTEMIS) studies have compared the low-molecular-weight heparins enoxaparin and dalteparin, and the specific factor Xa inhibitor fondaparinux, respectively, with placebo in acutely ill medical patients hospitalized with heart failure, respiratory failure, infectious disease, or inflammatory disease. All studies showed both a statistically significant reduction in the rate of venous thromboembolic events (as assessed by venography or compression ultrasonography) and a rate of major bleeding events that were comparable to placebo. The results of these studies support the evidence-based recommendations for systematic use of thromboprophylaxis in this setting. (*Clinical Cornerstone.* 2005;7[4]:16–22)

Pulmonary embolism (PE) is a leading cause of mortality in hospitalized patients, accounting for ~10% of all in-hospital deaths.[1] In the last 3 decades, great attention has been given to the prevention of venous thromboembolism (VTE) in patients undergoing surgery, and many good-quality clinical trials have placed the routine use of prophylaxis in such patients on a firm scientific footing. However, autopsy studies consistently find that 70% to 80% of all in-hospital deaths related to PE are not associated with surgical procedures but actually occur 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] More recently, Monreal et al[8] reported a more severe presentation and a significantly worse outcome in patients who developed VTE after an acute medical disease than in patients who developed VTE after surgery. Overall, prevention of VTE has been less extensively studied in medical patients than in surgical patients. However, in recent years a number of landmark studies[9–11] have consistently found that pharmacologic prophylaxis of VTE was indeed both safe and effective in the medical setting. As a result, evidence-based practice guidelines began to strongly recommend the use of pharmacologic prophylaxis in patients with acute medical diseases (eg, heart failure, acute respiratory disease, sepsis, cancer, and inflammatory bowel disease).[12] Despite this evidence, recent practice audits indicate significant underuse of thromboprophylaxis in medical patients.[13–15] Reasons for such underuse include, among others, the great heterogeneity of the population of medical patients that makes this group more difficult to target than surgical patients, concern about bleeding risk, and the lack of perception that VTE is a real issue.

THE EVIDENCE

Until 5 to 6 years ago, there was only limited evidence to support the use of thromboprophylaxis in medical patients. A number of small clinical trials conducted in a heterogeneous population and with heterogeneous study

KEY POINT

Autopsy studies consistently find that 70% to 80% of all in-hospital deaths related to PE are not associated with surgical procedures but actually occur in medical patients.

designs failed to provide convincing evidence of the efficacy of routine prophylaxis in hospitalized medical patients. The first of these studies was carried out with unfractionated heparin (UFH) administered BID or TID.[16–19] Following this, numerous studies have reported the use of several forms of low-molecular-weight heparin (LMWH). Two studies were conducted with dalteparin,[20,21] 4 with nadroparin,[22–25] and 4 with enoxaparin.[26–29] The results of these studies were conflicting and inconclusive. Only the results of a meta-analysis[30] of these studies and a number of subsequent large randomized trials[9,30–33] have convinced the clinicians of the need for prophylaxis in this setting. In a meta-analysis,[30] the use of pharmacologic prophylaxis, either LMWH or UFH, was shown to reduce the risk of deep vein thrombosis (DVT) by 50% to 60% and the risk of clinical and fatal PE by ~50% compared with placebo or no treatment. UFH and LMWH appeared to be similar in efficacy, but LMWH was safer, with ~50% reduction in the risk of major bleeding.

The first large, methodologically rigorous study of the use of thromboprophylaxis in medical patients was the prophylaxis in MEDical patients with ENOXaparin (MEDENOX) study.[32] In this study, 2 doses of enoxaparin, 20 mg and 40 mg administered for 6 to 14 days, were compared with 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 having very different risks for venous thrombosis, this trial included well-defined categories of patients (eg, patients with congestive heart failure, acute respiratory disease, acute infection without septic shock, acute rheumatic disease, or inflammatory bowel disease) with disorders that are known to put them at moderate risk for VTE (**Table**[10–11,32]). In this study, the occurrence of DVT was systematically evaluated with venography at the end of treatment. After 14 days, there was a statistically significant reduction in venous thromboembolic events in the group treated with enoxaparin 40 mg compared with placebo, but there was no reduction with enoxaparin 20 mg. Major bleeding rates and mortality rates were comparable among the 3 groups. At 110-day follow-up, there was no evidence of rebound in clinically detectable thromboembolic events. Subsequent subanalyses of the MEDENOX study showed that enoxaparin 40 mg was similarly effective among all subgroups of patients, with a relative risk reduction ranging from 52% in patients with acute rheumatic disorders to 75% in patients with acute respiratory failure,[31] and that major concomitant risk factors predisposing to VTE were previous VTE, concomitant acute infectious disease, malignancy, and age >75 years.[32]

KEY POINT

In a meta-analysis, the use of pharmacologic prophylaxis, either LMWH or UFH, was clearly shown to reduce the risk of DVT by 50% to 60% and the risk of clinical and fatal PE by ~50% compared with placebo or no treatment.

Subsequently, another LMWH, dalteparin, was assessed in a large, randomized, double-blind, controlled trial in the prevention of VTE in the medical population. In the Prospective Evaluation of Dalteparin Efficacy for PREVENTion of VTE in Immobilized Patients Trial (PREVENT), [10] 3706 patients randomly received SC dalteparin 5000 IU QD or placebo for up to 14 days (**Table**). In this study, the primary end point was the development of symptomatic DVT, fatal or nonfatal PE, sudden death, or asymptomatic proximal DVT detected by means of compression ultrasonography. The patient population was similar to that of the MEDENOX study.[32] In particular, 52% of patients had heart failure and 30% had respiratory disease. A statistically significant relative risk reduction (45%) was obtained in the primary end point with dalteparin compared with placebo (2.8% vs 5.0%), with no substantial difference in the rate of major bleeding events (0.5% vs 0.2%). In a subsequent subanalysis, the authors

of the PREVENT study assessed the efficacy and safety of dalteparin in the subgroups of obese patients, in whom potential decreased efficacy of the fixed-dose regimen was hypothesized, and of patients aged >75 years, in whom potential decreased safety was hypothesized.[23] The results of the analysis showed a nonstatistically significant relative risk reduction (0.64) in the primary end point in favor of dalteparin in the subgroup of obese patients and a statistically significant relative risk reduction (0.52) (95% CI, 0.31–0.87) in the subgroup of elderly patients. No difference in the rate of major bleeding events was observed between dalteparin and placebo in either group.

Finally, the ARixta for ThromboEmbolism prevention in a Medical Indications Study (ARTEMIS)[11] evaluated the efficacy and safety of fondaparinux, a synthetic inhibitor of factor Xa, in the prevention of VTE in medical patients. In this study conducted in 849 patients aged ≥60 years who were admitted because of heart failure, acute or chronic respiratory disease, acute infection, or acute inflammatory disease (**Table**), fondaparinux (2.5 mg/d SC) significantly reduced the rate of VTE compared with placebo, including both DVT and fatal PE, without increasing major bleeding events. The composite measure of venographically proven DVT and symptomatic DVT and/or PE was at baseline 10.5% to 5.6% at the end of study. The rate of major bleeding events was 0.2% in both groups.

Following the convincing results of these randomized controlled trials, international guidelines such as the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic Therapy[9] are now strongly recommending the use of pharmacologic prophylaxis, either low-dose UFH or LMWH, in patients with acute medical diseases (eg, heart failure or acute respiratory failure) and in patients who are bedridden and have 1 of the following risk factors: sepsis, active cancer, previous VTE, acute neurologic disease, or inflammatory bowel disease.[9]

KEY POINT

The ACCP guidelines strongly recommend the use of pharmacologic prophylaxis in patients with acute medical diseases (eg, heart failure or acute respiratory failure) and in patients who are bedridden and have 1 of the following risk factors: sepsis, active cancer, previous VTE, acute neurologic disease, or inflammatory bowel disease.

CONCLUSIONS

VTE is an important cause of morbidity and mortality in hospitalized medical patients. The results of recent

TABLE. STUDY POPULATIONS IN THE MEDENOX,[32] PREVENT,[10] AND ARTEMIS[11] STUDIES.

MEDENOX	PREVENT	ARTEMIS
Age ≥40 years	Age ≥40 years	Age ≥60 years
Expected bed rest ≥6 days	Expected bed rest ≥4 days	Expected bed rest ≥4 days
Recent immobilization ≤3 days	Recent immobilization ≤3 days	Length of recent immobilization not specified
Congestive heart failure (NYHA III–IV)	Congestive heart failure (NYHA III–IV)	Congestive heart failure (NYHA III–IV)
Acute respiratory disease	Acute respiratory disease	Acute or chronic respiratory disease
Acute infection*	Acute infection*	Acute infection†
Acute rheumatic disease*	Acute rheumatic disease*	Acute inflammatory disease†
Inflammatory bowel disease*	Inflammatory bowel disease*	

MEDENOX = MEDical patients with ENOXaparin; PREVENT = Prospective Randomized Evaluation of Dalteparin Efficacy for PREVENTion of VTE in Immobilized Patients Trial; ARTEMIS = ARixta for ThromboEmbolism prevention in a Medical Indications Study; NYHA = New York Heart Association.
*In addition, ≥1 of the following risk factors: age >75 years, cancer, previous venous thromboembolism, obesity, varicose veins, hormonal therapy, or chronic heart or lung disease.
†No additional risk factors required.

clinical trials show that VTE in medical patients is a preventable disease. Furthermore, these trials have better defined the target population and have provided important information on the risk of bleeding in these patients. The results were consistent among the studies, despite some differences in the designs and despite the different compounds assessed. Patient populations were similar in the MEDENOX and the PREVENT studies and slightly different in ARTEMIS, in which inclusion criteria were simplified. However, the same disease categories were represented in all studies. The primary end points of the studies were based on the results of venography in the MEDENOX study and in ARTEMIS and on the results of compression ultrasonography in the PREVENT study. These differences in the methods used to detect DVT explain why the rates of events differed among trials. However, the clinical relevance of asymptomatic DVT, either detected by venography or by compression ultrasonography, is well established. In all studies, the rate of major bleeding events was minimal and it was similar between the active drug and placebo. However, caution must be taken in the presence of impaired renal function and other risk factors for bleeding. Thus, the results of clinical studies of VTE prevention in medical patients clearly support the use of thromboprophylaxis in this setting.

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Dialogue Box

EDITORIAL BOARD

Although the meta-analysis by Mismetti et al demonstrated that unfractionated heparin (UFH) and low-weight-molecular heparin (LMWH) were comparable in preventing deep vein thrombosis (DVT) in medical patients, it also showed that LMWH was associated with a 50% lower risk of major bleeding. Is LMWH really that much safer than UFH?

TURPIE

No, I don't view the meta-analysis as conclusive in that regard. It is important to recognize that the studies included in the meta-analysis used varying dosages of LMWH. These doses included doses that were low enough to be ineffective against thrombosis; such doses, in turn, would naturally be associated with a lower risk for bleeding. The bottom line is that this may cause LMWHs to falsely appear safer in comparison to UFH than they actually are when used for prophylaxis.

EDITORIAL BOARD

What about in patients being treated for established DVT?

TURPIE

That's a different story. Pretty solid evidence exists that LMWHs are safer than UFH in patients with venous thromboembolism (VTE) since the doses used in such patients are much higher across the board.

EDITORIAL BOARD

As prophylactic agents, are UFH and LMWH comparable in terms of efficacy?

TURPIE

The meta-analysis certainly supports that. In addition, if you examine studies comparing them in specific settings, such as heart failure and respiratory failure, no statistically significant difference has been demonstrated between LMWH versus UFH given at a dosage of 5000 U SC TID. In patients who experienced a stroke, however, LMWH was found to be more effective than UFH in one study.

EDITORIAL BOARD

Can the higher percentage of symptomatic VTE cases seen among medical patients be attributable simply to there being more medical patients who are hospitalized than surgical patients?

TURPIE

That's an interesting thought. However, in point of fact, there are at least the same, if not more, surgical patients in hospitals than medical patients. Yet there are 4 times as many medical patients dying from pulmonary embolism (PE) than surgical patients. The higher risk seen in medical patients likely results from medical patients simply being sicker. A lot more surgical patients who are hospitalized are in good health since a number of young people come in for elective procedures. Overall, if one looks in terms of at-risk patients, fewer surgical patients are at risk for VTE than medical patients in the hospital.

EDITORIAL BOARD

Wouldn't that also explain why worse clinical outcomes are seen in medical patients with VTE?

AGENO

Exactly. Monreal et al simply confirmed the observation that medical patients in the hospital tend to be sicker than surgical patients. Such patients are at high risk for bleeding as well as at higher risk for DVT. In addition, when VTE occurs, the consequences are more severe.

EDITORIAL BOARD

Do medical patients require higher doses for DVT prophylaxis than surgical patients?

TURPIE

Yes, they do. The MEDENOX study compared 2 doses of LMWH, 20 mg and 40 mg, as prophylaxis against VTE. Although the 20-mg daily dose of enoxaparin has

Dialogue Box

been shown to be effective in moderate-risk surgical patients, this dose proved ineffective in medical patients in the MEDENOX trial. Instead, a 40-mg dose was required to be effective.

EDITORIAL BOARD

Is there a higher risk of converting a thrombotic stroke to a hemorrhagic one in the setting of an acute stroke without evidence of hemorrhage on CT scan of the brain?

AGENO

No. Prophylactic doses of LMWH or UFH appear safe in such patients. Therapeutic doses, on the other hand, would significantly increase the risk of bleeding in such patients.

EDITORIAL BOARD

What is meant by "rebound" when used in the setting of DVT prophylaxis?

TURPIE

The term *rebound* is somewhat a misnomer. Although there is evidence that there's an ongoing risk in medical patients, there's no evidence that the risk becomes greater in patients after DVT prophylaxis. What is seen is an ongoing or continuing risk, and the big question is: How long should we keep prophylaxis going? This issue is being looked at in a study called EXCLAIM, which is investigating the use of enoxaparin 1 month versus 1 week in medical patients.

EDITORIAL BOARD

The PREVENT trial seemed to suggest that the dosage may need to be higher in obese patients. What are your thoughts?

TURPIE

It's still unresolved. Most of the data do not support the use of dose adjustment, but I don't think the studies have been sufficiently powered to give us a firm answer to that one.

EDITORIAL BOARD

How does fondaparinux compare to LMWH in VTE prophylaxis in medical patients?

TURPIE

Although it has not yet been published, the ARTEMIS trial demonstrated a reduced risk of fatal PE in medical patients treated with fondaparinux compared with placebo. ARTEMIS was a prospective, randomized, double-blind trial and is the only study to show a reduced risk of fatal PE in medical patients. However, one really can't conclude that fondaparinux is better than heparin because there never has been a direct comparison between the 2 agents in this setting. What we can say is that they both are effective as DVT prophylactic agents and that prophylaxis is good.

EDITORIAL BOARD

What specific categories of medical patients warrant strong consideration for DVT prophylaxis during hospitalization?

TURPIE

A good reference would be a recent publication by Ander Cohen in the *Journal of Thrombosis and Haemostasis*, which really pinpoints the at-risk medical patients. Such patients include those with heart failure, respiratory failure, and acute infections.

AGENO

Stroke patients also should be added to that list.

Venous Thromboembolism in Medically Ill Patients: Identifying Risk and Strategies for Prevention

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Venous thromboembolism (VTE) is a condition that has multiple causes but few warning signs. Consequently, the 2 manifestations of VTE—pulmonary embolism and deep vein thrombosis—often go unpredicted. This is especially true for medical patients. Treatment guidelines indicate that most hospitalized patients should receive prophylaxis for VTE. This report discusses these guidelines, the high prevalence of VTE among medical patients, and clinical studies of thromboprophylaxis in medically ill patients.

VTE prophylaxis continues to be underutilized in medically ill patients. These patients are at significant risk of VTE and require prophylaxis, an objective that is supported by the recent guidelines of the American College of Chest Physicians. In addition, several lines of clinical evidence support the use of prophylaxis in this subgroup of patients. Improved systems are needed in medically ill patients to help improve outcomes and compliance for the use of VTE prophylaxis. (*Clinical Cornerstone.* 2005;7[4]:23–31)

Venous thromboembolism (VTE) is a condition that has multiple causes but few warning signs. Consequently, pulmonary embolism (PE) and deep vein thrombosis (DVT), the 2 components of VTE, often go unpredicted. This is especially true for medical patients, in whom thromboembolic risk has been less clearly established than for surgical patients.

Several factors are thought to be associated with an increased risk of VTE, including periods of reduced mobility, increasing age, major surgery, prior VTE, and chronic heart failure (**Table I**).[1] Strong risk factors for VTE include hip or knee replacement and major general surgery; weaker risk factors include increasing age and laparoscopic surgery. Given the wide range of risk associated with various factors, the decision to provide VTE prophylaxis should take into account the specific risk of each patient[1]; however, guidelines indicate that most hospitalized patients should receive prophylaxis for VTE. This report discusses these guidelines, the high prevalence of VTE among medical patients, and clinical studies of thromboprophylaxis in medically ill patients.

PREVALENCE OF VENOUS THROMBOEMBOLISM AMONG MEDICAL PATIENTS

In a typical hospital population, 78% of patients have ≥1 risk factors for VTE, and ~20% of patients have at least 3 risk factors.[2] Overall, the incidence of VTE among medically ill patients is estimated to be ~18% to 23% (**Figure**).[3]

The benefits of treating and preventing VTE in surgical patients are well established; however, many at-risk hospitalized medical patients do not appear to be receiving adequate prophylaxis. In 1995, Hirsch et al[4] reported that the rate of DVT was unexpectedly high in medical patients in the intensive care unit, despite the fact that prophylaxis was administered to 61% of the patients. DVT was detected with ultrasound in one third of 100 eligible patients over an 8-month period. About half of the cases involved proximal lower-extremity DVT. Furthermore, no difference in risk factors—including age, sex, body mass index, diagnosis of cancer, recent surgery, or duration of hospitalization before DVT detection—was observed among those who developed DVT versus those

TABLE I. RISK FACTORS FOR VENOUS THROMBOEMBOLISM (VTE).

Strong risk factors (odds ratio >10)
- Fracture (hip or leg)
- Hip or knee replacement
- Major general surgery
- Major trauma
- Spinal cord injury

Moderate risk factors (odds ratio 2–9)
- Arthroscopic knee surgery
- Central venous lines
- Chemotherapy
- Congestive heart or respiratory failure
- Hormone replacement therapy
- Malignancy
- Oral contraceptive therapy
- Paralytic stroke
- Pregnancy/postpartum
- Previous VTE
- Thrombophilia

Weak risk factors (odds ratio <2)
- Bed rest >3 days
- Immobility due to sitting (eg, prolonged car or air travel)
- Increasing age
- Laparoscopic surgery (eg, cholecystectomy)
- Obesity
- Pregnancy/antepartum
- Varicose veins

Reprinted with permission.[1]

who did not. Thus, the authors concluded that intensive prophylaxis regimens are warranted in this patient population.[4]

KEY POINT

Guidelines indicate that most hospitalized patients should receive prophylaxis for VTE.

CURRENT RECOMMENDATIONS OF THE AMERCIAN COLLEGE OF CHEST PHYSICIANS

Pharmacologic approaches currently indicated for thromboprophylaxis include unfractionated heparin (UFH); low-molecular-weight heparin (LMWH), such as enoxaparin and dalteparin; fondaparinux, an antithrombotic agent that specifically inhibits factor Xa; and vitamin K antagonists such as warfarin.

The Seventh American College of Chest Physicians' Conference on Antithrombotic and Thrombolytic Therapy recently updated evidence-based guidelines for the prevention of VTE.[5] Compared with previous approaches,[6] the new guidelines include stronger evidence-based recommendations for the use of VTE prophylaxis in various settings.[5] Notably, the new guidelines state that "all institutions should have a program in place that allows for the

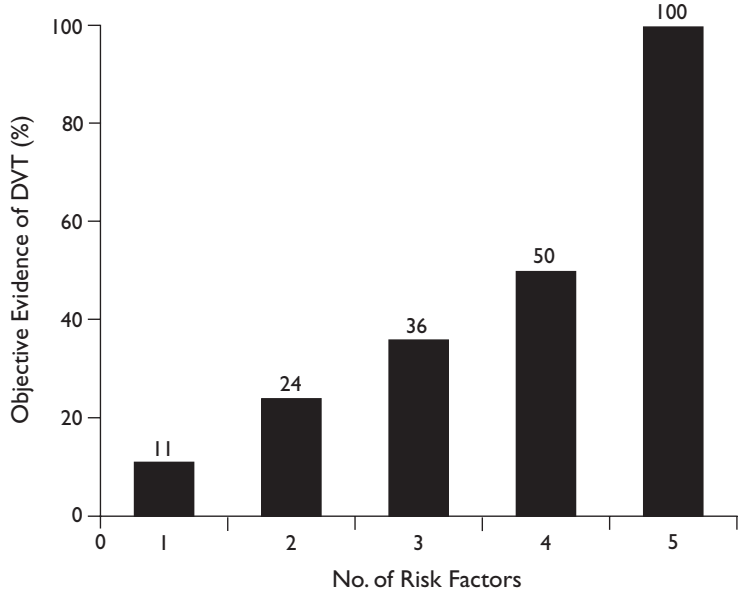

Figure. The proportion of patients with clinically suspected deep vein thrombosis (DVT) in whom the diagnosis was confirmed by objective testing increases with the number of risk factors. Data adapted with permission.[3]

evaluation of a patient's risk of developing VTE. If patients are found to be at risk of VTE, appropriate prophylaxis should be implemented." They also suggest that all patients admitted to the intensive care unit should be assessed for their risk of VTE, and most should receive thromboprophylaxis. In addition, all patients with at least 1 risk factor for VTE who have undergone trauma or who are confined to bed should receive thromboprophylaxis, as should acutely ill medical patients who have been admitted to the hospital with congestive heart failure or severe respiratory disease.

For surgical patients, low-dose UFH or LMWH should be used for moderate- and higher-risk patients, with the dose depending on the level of risk.[5] In addition, thromboprophylaxis should be used in all patients undergoing major gynecologic surgery or major, open urologic procedures. In patients undergoing hip or knee replacement surgery, LMWH, fondaparinux, or adjusted-dose vitamin K antagonists should be used for at least 10 days. For patients undergoing hip fracture surgery, low-dose UFH in addition to LMWH, fondaparinux, or vitamin K antagonists are recommended.

KEY POINT

The ACCP guidelines state that "all institutions should have a program in place that allows for the evaluation of a patient's risk of developing VTE. If patients are found to be at risk of VTE, appropriate prophylaxis should be implemented."

USE OF ANTITHROMBOTIC THERAPY: GUIDELINES VERSUS REALITY

A recent report suggests that thromboprophylaxis is significantly underused in US hospitals.[7] According to the researchers, a large proportion of hospitalized patients do not receive adequate antithrombotic therapy for prevention of thromboembolic disease. Tapson et al[7] randomly selected data from 3778 inpatient medical records at 38 US hospitals. Patients were undergoing treatment for atrial fibrillation, acute myocardial infarction, DVT, or PE. The study also included patients receiving thromboprophylaxis for total hip or knee replacement, or hip fracture surgery. Among patients with atrial fibrillation at high risk for stroke, just over half (54.7%) received warfarin, but ~20% received neither aspirin nor warfarin. Among patients with acute myocardial infarction, about one fourth did not receive aspirin when they arrived at the hospital. For orthopedic surgery procedures, ~85% of patients received prophylaxis with warfarin or a parenteral anticoagulant agent. Prophylaxis was discontinued in about half of the patients with PE and/or DVT before an international normalized ratio of ≥2.0 was achieved for ≥2 days. Moreover, patients with VTE rarely received bridge therapy (ie, an injectable anticoagulant agent plus warfarin) when leaving the hospital, despite the fact that the length of time to discharge was longer when patients received warfarin alone (4.0 vs 8.1 days; $P < 0.001$). Thus, antithrombotic use appears to vary depending on medical condition and is underused in some patients.

Arnold et al[8] reported that 17.4% of 253 objectively diagnosed cases could have been prevented had thromboprophylaxis guidelines been followed. Among the preventable cases, the most frequent reasons for insufficient prophylaxis were omission (47.7%), inadequate duration (22.7%), and incorrect type (20.5%) of prophylaxis. Common surgical and medical indications for thromboprophylaxis among the preventable cases included admission to the hospital for pneumonia, nonorthopedic surgery, and stroke with lower limb paralysis; common risk factors for VTE included obesity, recent immobility, and malignancy.

In an epidemiologic study that included 5451 patients with ultrasound-confirmed DVT, 2726 patients had their DVT diagnosed while in the hospital. Of those, only 42% received prophylaxis within the 30 days before diagnosis.[9] The 5 most frequent comorbidities among these patients were hypertension (50%), surgery within 3 months (38%), immobility within 30 days (34%), cancer (32%), and obesity (27%). Among the 1362 nonsurgical patients, the rate of prior prophylaxis was only 20% compared with 43% of the 1364 surgical patients. Thus, the results of this large study also indicate that thromboprophylaxis is considerably underused, especially among medical patients.

STRATEGIES FOR PREVENTING VENOUS THROMBOEMBOLISM IN MEDICAL PATIENTS

Evidence of the benefits of thromboprophylaxis in medical patients has been derived from smaller randomized trials that took place before the introduction of newer,

more effective therapies. Consequently, the effects of thromboprophylaxis for medical patients are less clear than they are for surgical patients.[10] Various studies are beginning to confirm the benefits of thromboprophylaxis specifically in the medical patient population. These include the prophylaxis in MEDical patients with ENOXaparin (MEDENOX) trial,[11] the PRophylaxis in Internal Medicine with Enoxaparin (PRIME) study,[12] the thromboembolism PRevention IN Cardiopulmonary diseases with Enoxaparin (PRINCE) study,[13] the Prospective Evaluation of Dalteparin Efficacy for PREVENTion of Venous Thromboembolism in Immobilized Patients (PREVENT) study,[14] and the ARixtra for ThromboEmbolism prevention in a Medical Indications Study (ARTEMIS).[15] Collectively, the findings suggest that LMWH (enoxaparin 40 mg or dalteparin 5000 IU SC QD for 10 days), as well as fondaparinux 2.5 mg SC QD for 10 days, demonstrate a favorable risk/benefit ratio for the prevention of VTE in acutely ill medical patients.[3]

In the landmark MEDENOX trial, 2 doses of enoxaparin (20 and 40 mg/d) were compared with placebo in medical patients.[11] Prophylactic treatment with 40 mg/d of enoxaparin given SC was found to significantly reduce the risk of VTE compared with placebo (5.5% for enoxaparin vs 14.9% for placebo; relative risk [RR], 0.37; 97.6% CI, 0.22–0.63; $P < 0.001$). In addition, the incidence of VTE at day 14 was significantly lower for patients receiving enoxaparin 40 mg compared with placebo ($P < 0.001$ for all VTE, and $P = 0.037$ for proximal DVT), and this benefit was maintained at 3 months. A subsequent analysis of data from the MEDENOX trial also indicated that the risk of VTE was increased in patients with acute infectious disease, cancer, age >75 years, and a history of VTE (**Table II**).[16]

The PREVENT study compared dalteparin with placebo in the prevention of VTE in 3706 medical patients. Patients were randomly assigned to receive either dalteparin 5000 IU SC QD or placebo for 14 days.[14] The inci-

TABLE II. INCIDENCE OF VENOUS THROMBOEMBOLISM (DAYS 1–14) BY REASON OF ILLNESS.

	No. (%) of Patients/Events*		
Illness	All (N = 866)	Placebo Group (n = 288)	Enoxaparin Sodium Group (40 mg) (n = 291)
Heart failure			
Yes	34/290 (11.7)	14/96 (14.6)	4/99 (4.0)
No	68/576 (11.8)	29/192 (15.1)	12/192 (6.3)
NYHA class III			
Yes	23/217 (10.6)	9/73 (12.3)	4/78 (5.1)
No	79/649 (12.2)	34/215 (15.8)	12/213 (5.6)
NYHA class IV			
Yes	11/73 (15.1)	5/23 (21.7)	0/21 (0)
No	91/793 (11.5)	38/265 (14.3)	16/270 (5.9)
Acute respiratory disease			
Yes	42/457 (9.2)	20/153 (13.1)	5/153 (3.3)
No	60/409 (14.7)	23/135 (17.1)	11/138 (8.0)
Acute infectious disease			
Yes	64/463 (13.8)	24/155 (15.5)	10/159 (6.3)
No	38/403 (9.4)	19/133 (14.3)	6/132 (4.5)
Acute infectious and respiratory disease			
Yes	27/239 (11.3)	13/79 (16.5)	4/88 (4.6)
No	75/627 (12.0)	30/209 (14.3)	12/203 (5.9)
Acute rheumatic disease			
Yes	14/78 (17.9)	6/29 (20.7)	2/20 (10.0)
No	88/788 (11.2)	37/259 (14.3)	14/271 (5.2)
Inflammatory bowel disease			
Yes	0/5 (0)	0/1 (0)	0/3 (0)
No	102/861 (11.8)	43/287 (15.0)	16/288 (5.6)

NYHA = New York Heart Association.
*Number of patients in subgroup/number of venous thromboembolic events.
Reprinted with permission.[16]

KEY POINT

Collectively, study findings suggest that LMWH, as well as fondaparinux, demonstrate a favorable risk/benefit ratio for the prevention of VTE in acutely ill medical patients.

dence of VTE was 4.96% in the placebo group versus 2.77% in the dalteparin group (RR reduction, 45%; $P < 0.002$). Likewise, the ARTEMIS trial compared fondaparinux with placebo in acutely ill, elderly medical patients.[15] The incidence of VTE at day 15 was 10.5% in the placebo group versus 5.6% in the fondaparinux group (RR reduction, 49.5%; $P < 0.003$).

Enoxaparin has also been compared in head-to-head trials with UFH. The PRIME study, a randomized, double-blind controlled trial comparing enoxaparin 40 mg/d with UFH TID in a high-risk group of 959 hospitalized medical patients, found that enoxaparin was comparable to UFH in preventing VTE, with fewer adverse events.[12] Similarly, the PRINCE study compared the efficacy and safety of 10 days of enoxaparin (40 mg/d SC) versus UFH (5000 IU TID SC) in 665 medical patients with severe cardiopulmonary disease.[13] As with the PRIME study, the results indicated that enoxaparin was as effective as UFH 5000 IU given TID.

Enoxaparin has also been found to be superior to UFH in medical patients who are at increased to high risk of VTE.[17] Harenberg et al[17] analyzed data from patients with severe respiratory disease, severe heart failure, or acute ischemic stroke. A total of 877 patients received either 40 mg enoxaparin QD or 5000 IU UFH TID. Among the 630 patients eligible for the efficacy analysis, thromboembolic events with subsequent death occurred in 15.6% of the patients in the enoxaparin group compared with 22.1% in the UFH group. Risk of VTE was highest among patients with acute ischemic stroke, followed by patients with severe heart failure and severe respiratory disease. Bleeding events occurred in 1.8% of the enoxaparin group versus 3.2% of the UFH group.

Finally, the ongoing EXtended CLinical Prophylaxis in Acutely Ill Medical Patients with Prolonged Immobilization Study[18] will help clarify the benefits of extended prophylaxis among medical patients. This study is assessing the role of extended prophylaxis with enoxaparin among ~5800 medical patients. Patients will receive enoxaparin 40 mg SC QD versus placebo for 28 days after 10 days of enoxaparin. Study end points include the incidence of ultrasound-confirmed VTE, major bleeding, and mortality.

CONCLUSIONS

Guidelines indicate that most hospitalized patients should receive prophylaxis for VTE; however, prophylaxis continues to be underutilized in medically ill patients. The decision to provide prophylaxis should take into account the specific risk of each patient and all institutions should have a program in place that evaluates a patient's risk of developing VTE.

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Dialogue Box

EDITORIAL BOARD

To what do you attribute the 18% to 23% incidence of venous thromboembolism (VTE) seen in medically ill patients in the hospital setting?

WHEELER

A number of factors play a role. The medical population has always been an underappreciated at-risk group. Although historically they may have been less ill than their surgical counterparts, this is clearly no longer the case. These days medical patients who make it into our hospitals are substantially more ill than they were 20 years ago, both acutely and chronically, since the threshold for getting through the doors of most hospitals has gone up. Another factor is we simply discharge patients substantially sooner than we used to. By discharging patients earlier, the level of severity of illness in hospitalized medical patients is higher. Although studies show varying risks of VTE across different populations within the hospital (with probably some of the highest-risk medical patients being those with congestive heart failure, chronic obstructive lung disease, and cancer), most medical patients in the hospital have multiple risk factors, and the more risk factors you have, the higher the risk.

EDITORIAL BOARD

Why the discrepancy between the baseline 18% to 23% figure you cited and the 5% to 10% incidence seen in placebo groups in the ARTEMIS and PREVENT trials?

WHEELER

Two possible differences are the populations studied and the method used to detect deep vein thrombosis (DVT). In trials such as these, subjects at the highest risk for the disease are invariably excluded from study. For example, some patients (such as those with advanced cancer or in the intensive care unit) may be perceived to be at such high risk that researchers determine it would be unethical to include them in a placebo-controlled trial. The second factor lies in differences in the varying sensitivities of the tests used to detect DVT. For example, if ultrasound is used, you might find an overall incidence of the disease somewhere between 5% and 10%. In those same patients, when using a more sensitive test such as contrast venography, you might find an incidence between 15% and 20%. If you use an investigative tool capable of detecting very small clots, such as radiolabeled fibrinogen scanning, you might find clots in 25% or 30% of these patients.

EDITORIAL BOARD

How do the different DVT prophylactic options compare with regard to efficacy?

WHEELER

If all things were equal, the greatest risk reduction for DVT has been shown with low-molecular-weight heparin, followed closely by unfractionated heparin that, when given TID in a fixed dose, reduces risk by about two thirds. Next best would be pneumatic compression devices, which fail roughly 50% of the time. Elastic stockings provide a 25% to 30% risk reduction.

EDITORIAL BOARD

Since none of these methods are wholly effective, should multiple prophylactic measures be considered in patients felt to be at particularly high risk?

WHEELER

That is a consideration. Let's say patients have a 60% chance of getting a calf DVT from a hip replacement procedure. With 1 intervention, I might be able to cut that in half—down to 30%. Only half of these (15%) will propagate into the thigh. Half of these (7%) become pulmonary emboli. Most of these VTE cases will be asymptomatic, with maybe 10% of them fatal, which comes to 1 in 100 patients provided the prophylactic measure has a fatality. Some people would say that 1 in 100 is good enough. Others would instead maintain that when you have a very high-risk patient (such as patients undergoing joint replacement, hip fracture surgery, or a quadriplegic patient following

Dialogue Box

trauma), you should use 2 methods. Some data exist that the so-called "belt and suspenders" strategy of adding a mechanical device to chemical anticoagulation is more effective than either method alone.

EDITORIAL BOARD

Please discuss further the rationale for continuing DVT prophylactic therapy in patients following hospital discharge.

WHEELER

There are 6 published studies in the orthopedic literature looking at extending DVT prophylaxis after discharge in patients following high-risk procedures such as knee replacement, hip replacement, and hip-fracture surgery. All of these studies were relatively consistent in showing that extending prophylaxis, either for 3 or 4 weeks, reduced the number of symptomatic clots that occurred and at least 1 study actually claimed a mortality benefit. This would seem almost intuitive, seeing that in the past these patients typically would have spent 2 weeks in the hospital following hip replacement and would have been offered DVT prophylaxis during that time. In my hospital, a patient who receives a hip replacement now may be discharged in 3 days, reducing the period of DVT prophylaxis from 2 weeks down to 3 to 4 days. That's likely where the benefit comes—extending prophylaxis a little bit longer into the recovery time at home, where the patient is still relatively immobile with still-resolving thrombogenic postsurgical changes. Another area of potential benefit is in oncology patients after extensive intra-abdominal and pelvic cancer resection. The ongoing EXCLAIM trial may be more relevant to the average practitioner because it's looking at a group of patients who internists and family doctors are much more likely to see—people in the hospital with congestive heart failure, chronic obstructive pulmonary disease, pneumonia, or rheumatologic disease who are being discharged with the eventual hope that someday they're going to improve but who still aren't fully ambulatory. With regard to the latter, patients in the study are being stratified by their levels of activity, such as whether they can walk to the bathroom or not.

EDITORIAL BOARD

Is there something about hospitalization that makes hospitalized medical patients at greater risk for DVT than the same patients in the nursing home setting?

WHEELER

That's a very common question I receive from internists who have difficulty seeing the need for DVT prophylaxis in a patient admitted from a nursing home, whether it be for urinary tract infection with hypotension, aspiration pneumonitis, or bed sores with cellulitis. Since such patients look the same to them in the hospital as they did in the nursing home, they sometimes have a hard time seeing why they should be offered DVT prophylaxis. My response is the patient must really not look the same; otherwise, they wouldn't have been admitted to the hospital. There had to be something different about the patient—whether it be the fever or leukocytosis or dyspnea/hypoxia—that made you concerned enough to put the patient in the hospital.

EDITORIAL BOARD

Are you saying that hospitalization is an indicator of a worsening of 1 or more components of Virchow's triad?

WHEELER

Absolutely. There was an article by John Heit a number of years ago that provided a 25-year retrospective of all cases of VTE disease diagnosed in Olmstead County. He showed that the disease frequency was roughly 200 times higher among hospitalized patients than those who were ambulatory. Interestingly, about half of all the cases diagnosed outside the hospital occurred in patients who had been in a hospital or a nursing home in the preceding 90 days.

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From the standpoint of cancer as a risk factor, are there some tumors that are so thrombogenic that you would be inclined to initiate DVT prophylaxis?

Dialogue Box

WHEELER

I would say any metastatic carcinoma. Of the cancers I see, the ones most commonly associated with thromboembolic disease are lung, breast, pancreas, and colon. I don't think there's anything really special about these cancers except possibly lung carcinoma. We tend to see a lot of patients with lung carcinoma and thromboembolic disease, but this may be a little bit unfair because, if you've got lung cancer, there's a good chance you've also got other risk factors such as chronic obstructive lung disease with older age and reduced mobility. These patients might also have chemotherapy or radiation as risk factors. At least in my practice, thromboembolic disease in patients who have lymphoma or leukemia is a relatively uncommon event.

Venous Thromboembolism Prophylaxis Guidelines: Use by Primary Care Physicians

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Venous thromboembolism (VTE), a prevalent, costly medical condition, is one of the most common causes of death in the United States. Although risk factors for VTE are well known, thromboembolic events cannot be predicted because patients are asymptomatic and screening methods have limitations. Anticoagulant therapy (eg, low-molecular-weight heparin, unfractionated heparin, selective factor Xa inhibitors) has proved effective for preventing thromboembolism, including deep vein thrombosis and pulmonary embolism. While quality care for VTE entails prophylaxis for all relevant patients, many high-risk patients are undertreated or treated incorrectly. Both primary and secondary prevention of VTE remain inadequate for several reasons, including lack of awareness of the American College of Chest Physicians guidelines, of the seriousness of VTE, of the benefits of prophylaxis, and of the relatively low risk of bleeding complications. To provide appropriate treatment, physicians must assess the numbers and types of risk factors for each patient, the underlying illness or surgical procedure, and the benefits and risks of possible therapies. The problem of VTE will grow as the US population ages, as surgery is performed on increasingly sick patients, and as the length of hospital stays continues to decrease. (*Clinical Cornerstone.* 2005;7[4]:32–38)

Venous thromboembolism (VTE), a prevalent, costly medical condition,[1] is one of the most common causes of death in the United States.[2] VTE causes an estimated 300,000 hospital admissions annually in the United States,[3] and patients hospitalized for other reasons typically have at least 1 risk factor for VTE.[1,4] Deep vein thrombosis (DVT) occurs in 10% to 60% (depending on the surgical procedure) of hospitalized patients who do not receive prophylaxis, and pulmonary embolism (PE) causes ~10% of all hospital mortality.[1] The risk of thromboembolic events continues after hospital discharge.[1] The costs of diagnostic testing, hospitalization, and treatment of the condition and its complications are enormous.[1]

Although risk factors for VTE are well known, thromboembolic events cannot be predicted.[1] Testing for DVT is problematic because of asymptomatic cases and limitations of various screening methods.[1] Fatal PE usually occurs unexpectedly,[1] and at least 75% of these deaths involve patients who have not recently undergone surgery.[1,5,6]

Anticoagulant therapy has proved effective for preventing both venous and arterial thromboembolism. Multiple well-designed studies have confirmed that thromboprophylaxis decreases the risk of DVT and PE without causing clinically important bleeding.[1] For example, a retrospective study of US hospitals showed a 70% reduction in the risk of VTE among inpatients treated with enoxaparin (a low-molecular-weight heparin [LMWH]) compared with untreated patients.[4] Likewise, a meta-analysis showed that LMWH or unfractionated heparin (UFH) reduced the risk of DVT by 50% to 60%.[6] Comparable or higher reductions in the risk of VTE were observed with the use of UFH in patients with acute myocardial infarction or stroke[6] and with warfarin for the prevention of stroke.[7]

Accordingly, the American College of Chest Physicians (ACCP) revised its guidelines[1] for VTE prevention in 2004. This article focuses on the practical application of these guidelines by primary care physicians.

KEY POINT

Multiple well-designed studies have confirmed that thromboprophylaxis decreases the risk of DVT and PE without causing clinically important bleeding.

QUALITY CARE AND VENOUS THROMBOEMBOLISM PROPHYLAXIS

Quality care is defined in several ways. Physicians judge quality based on accurate diagnosis, appropriate treatment, and use of rigorous clinical trials to inform medical decisions.[8] A comprehensive review of the topic concluded that physicians, nurses, administrators, and patients agree on several quality criteria.[9] Among these are competent staff; ample resources; cost-effective and efficient care; accurate diagnosis, treatment, and monitoring; adherence to best practices and protocols; patient-centered care; good health outcomes; and ongoing quality control.[9] To promote best practices for VTE prevention, as for any medical condition, guidelines must be developed, disseminated, tested, and implemented.[10]

Quality care for VTE entails prophylaxis for all relevant patients because the literature demonstrates the effectiveness of prophylaxis, because standards of care exist,[1] and because surgical and medical patients have a high risk of VTE.[6] However, many acutely ill patients are undertreated during hospitalization[2] and in community practice.[4] Only about one third of high-risk patients are prescribed anticoagulants to prevent VTE.[5] The reason may be a lack of diagnosis. Although VTE is suspected before death in ~65% of postsurgical patients who die of PE, VTE is suspected in only ~25% of medical (nonsurgical) patients who die of PE.[2,5] Autopsy studies confirm high rates of unsuspected PE.[2]

When thrombotic disease is confirmed, patients often receive incorrect or insufficient prophylaxis.[11] In a retrospective study of antithrombotic therapy in 38 US hospitals between 2000 and 2003, only 55% of high-risk patients with atrial fibrillation received warfarin and 21% received no anticoagulant or aspirin.[11] In fact, treatment of atrial fibrillation to prevent stroke may be least optimal in patients at highest risk for stroke—the elderly.[7] In the hospital study, only 76% of patients with acute myocardial infarction were treated with aspirin at admission.[11] Among patients with DVT or PE, only 60% received LMWH or UFH and nearly half had heparin discontinued before treatment goals were reached (international normalized ratio [INR] ≥2.0 for 2 days).[11] VTE patients were typically discharged without bridge therapy (ie, parenteral anticoagulant plus warfarin). Among orthopedic surgery patients, 86% received prophylaxis.[11]

KEY POINT

Quality care for VTE entails prophylaxis for all relevant patients because the literature demonstrates the effectiveness of prophylaxis, because standards of care exist, and because surgical and medical patients have a high risk of VTE.

Thus, both primary and secondary prevention of VTE remain inadequate.[11] Undertreatment may be due to a lack of awareness of the ACCP guidelines,[1] of the importance of VTE, of the benefits of prophylaxis, and of the relatively low risk of bleeding complications.[11,12] Physicians must be educated about treatment guidelines and the risks of therapy and must have adequate resources for prescribing and follow-up.[6,11,12]

KEY POINT

Both primary and secondary prevention of VTE remain inadequate.

PRIMARY CARE PHYSICIANS: PRACTICAL APPLICATION OF THE GUIDELINES

To provide appropriate treatment, physicians must assess the numbers and types of risk factors in each patient, the underlying illness or surgical procedure, and the benefits and risks of possible therapies.[1,2] Knowledge of the literature and clinical judgment play important roles.[1]

Risk Factors

The ACCP guidelines[1] describe treatment recommendations for patients in 8 high-risk groups: major general surgery (vascular, gynecologic, urologic, and

laparoscopic procedures); orthopedic surgery (hip, knee, spine, and lower extremity); neurosurgery; trauma, spinal cord injury, and burns; acute medical conditions; cancer; critical care; and long-distance travel. Surgery, particularly orthopedic surgery, is a well-known risk factor for VTE.[1]

Major medical risk factors for VTE include age, obesity, immobilization, smoking, varicose veins, cancer and its treatment, lower-extremity paresis, congestive heart failure, respiratory failure, severe infection, trauma, pregnancy, estrogen use in hormone replacement or oral contraceptives, acute rheumatic disease, inflammatory bowel disease, thrombophilic states, central venous catheter, and history of VTE.[1,6] The risk of stroke in patients with atrial fibrillation increases with previous embolic events (eg, stroke, acute myocardial infarction, transient ischemic attack), hypertension, left ventricular dysfunction, age >75 years, rheumatic mitral valve disease, or prosthetic heart valve; risk is increased to a lesser extent by age 65 to 75 years, diabetes, and coronary artery disease without left ventricular dysfunction.[11]

Thrombotic risk increases with a higher number of risk factors,[6] and certain risk factors "weigh" more than others.[13] One hierarchy assigns a score of 3 for cancer, history of VTE, and hypercoagulable states; a score of 2 for major surgery; and a score of 1 for advanced age, obesity, bed rest, and use of estrogen.[13] A total score of 4 is considered an increased risk. Classification schemes for surgical and medical patients are shown in **Table I**[1] and **Table II**,[5] respectively.

Choice of Thromboprophylaxis

VTE prophylaxis should be noninvasive when patient risk is low. Early ambulation of hospitalized patients is encouraged, and compression stockings can be used if ambulation is not possible.[1,5] Improper fit and poor compliance are drawbacks to the use of these stockings.[1] Aspirin alone is not recommended for any VTE patients (in contrast to atherosclerosis patients) because of inadequate effectiveness and the risk of bleeding.[1]

In general, the ACCP guidelines[1] call for routine prophylaxis with LMWH or low-dose UFH for moderate-risk and high-risk surgical (**Table I**) and medical patients. Mechanical devices, although not well studied in medical patients, are considered useful for high-risk cases in combination with anticoagulants[1] or alone if anticoagulants are contraindicated.[1,5] LMWH is now considered superior to UFH because of equivalent effectiveness, lower risk of bleeding, and other adverse effects (eg, heparin-induced thrombocytopenia), longer half-life, simpler weight-based dosing, and less need for monitoring.[1,6,14,15] However, the various LMWHs have different pharmacologic characteristics and should not be considered interchangeable.[1] The ACCP guidelines[1] also recommend vitamin K antagonists in certain cases (eg, orthopedic surgery and trauma). The selective factor Xa inhibitor fondaparinux may be used for orthopedic procedures[1] and in acutely ill medical patients.[2]

The newest agent is ximelagatran, a selective factor Xa inhibitor.[7] Benefits of ximelagatran include good efficacy for prevention of VTE and stroke, oral administration BID, predictable pharmacokinetic characteristics,

TABLE I. THROMBOEMBOLISM RISK AND ASSOCIATED PROPHYLAXIS IN SURGICAL PATIENTS.

Risk	Clinical Characteristic	Prophylaxis
Low	• Minor surgery at age <40 years with no other risk factors	None; early mobilization
Moderate	• Minor surgery with other risk factors • Surgery at age 40–60 years with no other risk factors • Major surgery at age <40 years with no other risk factors	LDUH 5000 U q12h, LMWH (≤3400 U/d), GCS, or IPC
High	• Minor surgery at age >60 years or other risk factors • Major surgery at age 40–60 years with other risk factors (eg, previous VTE, cancer, hypercoagulability)	LDUH 5000 U q8h, LMWH (>3400 U/d), or IPC
Very high	• Surgery with multiple risk factors (eg, age >40 years, cancer, previous VTE) • Hip or knee arthroplasty, hip fracture surgery • Major trauma or spinal cord injury	LMWH (>3400 U/d), fondaparinux, oral VKAs (to INR 2.0–3.0), or IPC/GCS + LDUH/LMWH

LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; GCS = graduated compression stockings; IPC = intermittent pneumatic compression; VTE = venous thromboembolism; VKA = vitamin K antagonist; INR = international normalized ratio. Adapted with permission.[1]

TABLE II. THROMBOEMBOLISM RISK IN MEDICAL PATIENTS.

Risk	Clinical Characteristic
Low (<10%)	• Minor illness (eg, uncomplicated pneumonia, cellulitis)
Moderate (10%–30%)	• Major illness (eg, heart or lung disease, cancer, inflammatory bowel disease, rheumatologic disease, severe infection), age >70 years
	• Minor illness plus thrombophilia or previous VTE
High (>30%)	• Lower-extremity paralysis (stroke, hemiplegia)
	• Major illness plus thrombophilia or previous VTE

VTE = venous thromboembolism.
Adapted with permission.[5]

wide therapeutic range, few food or drug interactions, fewer adverse effects than heparins, and less need for coagulation monitoring, although elevated liver enzyme activities have been observed.[7] Its role in treatment and prophylaxis awaits future studies.

Acute Venous Thromboembolism

Acute cases of VTE are typically treated in the hospital with intravenous UFH or LMWH for 5 to 10 days, with concomitant warfarin added until a therapeutic INR is reached for at least 2 days.[7,15] After this period, heparin is discontinued.[15] Oral warfarin can be taken for secondary prevention for 3 to 12 months, with a target INR of 2.0 to 3.0.[7]

Patients with a previous acute VTE event have a high risk of future thromboembolic events. The best approach for secondary prevention is to evaluate risk factors for recurrence in individual patients and to provide long-term prophylaxis for those at high risk.[7] As always, the benefit of treatment must be weighed against bleeding risk and patient compliance.[7]

KEY POINT

Patients with a previous acute VTE event have a high risk of future thromboembolic events.

Dose and Duration

In general, physicians should prescribe the manufacturer's recommended dose.[1] Typical doses are listed in **Table III**.[3,14,15] Often a higher dosage provides greater efficacy without increased risk of bleeding (eg, heparin 5000 U TID vs 5000 U BID; dalteparin 5000 U/d vs 2500 U/d).[1] Obese patients may need higher doses than nonobese patients.[6]

No guidelines exist for the optimal duration of VTE thromboprophylaxis, so the duration of treatment should be individualized[1,2] based on the patient, drug, and indication. A suggested duration for acute medical illness is 10 days of therapy with enoxaparin 40 mg/d SC, dalteparin 5000 IU/d SC, and fondaparinux 2.5 mg/d SC.[2] Warfarin 1 mg/d for 6 weeks has been used for VTE prevention in cancer.[2] The duration of use in clinical practice is often inadequate.[11]

Prophylaxis must be continued after hospital discharge to prevent recurrent thromboembolic events and postthrombotic syndrome.[1,2] The risk of DVT is greatest in the first 2 weeks after surgery and fatal PE may occur even later.[1] Bridge therapy should be given.[11] Prophylaxis may be needed for about 1 month after orthopedic surgery.[1] Patients with chronic medical conditions or previous VTE events also require long-term oral anticoagulant therapy.[16]

KEY POINT

Prophylaxis must be continued after hospital discharge to prevent recurrent thromboembolic events and postthrombotic syndrome.

Risks of Treatment, Contraindications, and Monitoring

Bleeding and thrombocytopenia are potential adverse effects of heparin treatment.[5] Platelet counts should be monitored regularly during LMWH therapy.[2] Heparin dosing must be adjusted to maintain a therapeutic activated partial thromboplastin time (eg, an activated partial thromboplastin time patient/control ratio of 1.5–2.5).[3]

Special populations require extra vigilance. Patients with renal insufficiency, especially the elderly, should be treated with caution because many anticoagulants (eg, LMWHs, fondaparinux, direct thrombin inhibitors) are cleared through the kidneys, and drug accumulation may increase the risk of bleeding.[1,2] Anticoagulants must be used with care in patients undergoing neuraxial anesthesia or analgesia.[1] Vitamin K antagonists such as warfarin, in addition to increasing the bleeding risk, interact with several foods and other drugs and have a narrow therapeutic range, so coagulation indices must be monitored and doses adjusted accordingly.[7,16] Home-based therapy is contraindicated in certain patients.[11,15,17]

HOSPITAL PROTOCOLS FOR VENOUS THROMBOEMBOLISM TREATMENT AND DEEP VEIN THROMBOSIS PREVENTION

Use of Clinical Guidelines for Hospitalized Patients

Data indicate that when hospitals adopt clinical guidelines, patient care improves and cost-effectiveness rises.[14,18] The effect of anticoagulant prescribing guidelines both before and after implementation was evaluated in 2 groups (n = 246 each) of patients at risk for VTE in 15 US hospitals.[14] Less than 1 year after adoption, the guidelines significantly increased the rate of appropriate prescribing from 60% to 87% ($P < 0.001$), reduced the number of adverse events, and decreased overall medical costs.[14] Pocket guides have also been developed as a simple and convenient reminder of VTE prophylaxis.[12]

Computerized guidelines also enhance understanding of and adherence to clinical protocols through monitoring and reminder systems.[10] At one hospital, a computerized reminder system was linked to the patient database to identify patients at high risk of VTE (at least 4 of 8 risk factors).[13] Patients in the intervention group (n = 1255; 1 electronic alert) were more likely to receive prophylaxis than those in the control group (n = 1251) (34% vs 15%; $P < 0.001$). The intervention group also had a 41% lower rate of DVT and PE at 90 days ($P = 0.001$), with no difference in bleeding complications or mortality.

Outpatient Treatment

Outpatient treatment of DVT with subcutaneous LMWH is considered effective and safe, potentially more cost efficient than inpatient treatment with intravenous UFH, and more satisfactory to most patients.[15,18] A clinical pathway was developed at a hospital to enhance

TABLE III. TYPICAL DOSES OF ANTICOAGULANTS USED FOR THROMBOPROPHYLAXIS.

Indication	Reference	Drug	Dose
DVT treatment	3	Heparin IV	5000 U bolus, then 32,000 U q24h IV infusion, or 35,000–40,000 U q24h SC, with infusion titrated to therapeutic aPTT
	15	Dalteparin SC	200 IU/kg q24h or 100 IU/kg q12h, for 5–7 days, with warfarin
	15	Enoxaparin SC	1 mg/kg q12h or 1.5 mg/kg q24h, for 5–7 days, with warfarin
	15	Tinzaparin SC	175 IU/kg q24h, for 5–7 days, with warfarin
Unstable angina; AMI without thrombolytics	3	Heparin IV	5000 U bolus, then 32,000 U q24h IV infusion, titrated to therapeutic aPTT
AMI with thrombolytics	3	Heparin IV	5000 U bolus, then 24,000 U q24h IV infusion, titrated to therapeutic aPTT
DVT/PE prophylaxis	3	Heparin SC	5000 U q8–12 h, or a low dose adjusted to therapeutic aPTT
DVT/PE prophylaxis; treatment of ACS	14 14 14	Warfarin PO Enoxaparin SC Dalteparin SC	Titrated to therapeutic INR 30 mg q12h; 40 mg q24h 2500 IU q24h; 5000 IU q24h

DVT = deep vein thrombosis; aPTT = activated partial thromboplastin time; AMI = acute myocardial infarction; PE = pulmonary embolism; ACS = acute coronary syndrome; INR = international normalized ratio.[3,14,15]

the use of outpatient LMWH with enoxaparin for patients with DVT in an emergency department.[17] The protocol included checklists for exclusion criteria, implementation steps, laboratory tests, dosing guidelines for enoxaparin and warfarin, and follow-up recommendations; patients received educational and clinical support.[17] Most of the eligible patients (74%) were started on the outpatient therapy, but further education was deemed necessary for patients and clinicians to increase enrollment in the program.[17] Although LMWH costs more than UFH,[15] the home treatment saves money overall by avoiding unnecessary hospitalization.[15,17]

Other studies show that patients receiving long-term oral anticoagulant therapy are capable of monitoring INRs and managing dosing at home, analogous to the self-care required for diabetes.[16] Current coagulation monitors for home use measure INR accurately, and home monitoring improves quality of life and saves money over time.[16]

Disadvantages exist with home self-care, however. Many health plans do not reimburse for outpatient treatment.[15] Patients must be selected carefully, educated about the proper use of LMWH and warfarin, warned about adverse effects, and monitored.[15] Some patients are unable to self-inject SC LMWH.[15,17] INR must be measured during the transition to warfarin therapy, although monitoring of anti-factor Xa activity is controversial.[15] Home-based therapy with VTE prophylaxis is contraindicated in patients with low platelet count, active bleeding or risk of bleeding, heparin sensitivity, use of aspirin or anticoagulants, pregnancy or lactation, renal insufficiency, recent surgery, and severe hypertension.[11,15,17]

SUMMARY

Studies show inadequate treatment of high-risk VTE patients. Physicians must administer prophylaxis for VTE when appropriate for at least 3 reasons: VTE is a prevalent, preventable, and often silent condition; the first presentation of VTE may be a fatal PE; and treatment guidelines promote this as the standard of care.[5] Programs should continue to educate physicians about the necessity of prophylaxis and the relative safety of anticoagulants. Hospitals should adopt clinical guidelines to improve patient care and to monitor efficacy. The problem of VTE will only grow as the US population ages, as surgery is performed on increasingly sicker patients, and as the length of hospital stays continues to decrease.

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Pharmacologic Therapy for the Management of Thrombosis: Unfractionated Heparin or Low-Molecular-Weight Heparin?

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Heparin and heparin-derived drugs play a major therapeutic role in thrombotic and cardiovascular disorders. Infusion of unfractionated heparin (UFH) followed by warfarin has traditionally been the standard pharmacologic therapy for treatment of venous thromboembolism (VTE), which includes both deep vein thrombosis and pulmonary embolism, and for initial therapy of non–ST-elevation (NSTE) acute coronary syndrome (ACS). More recently, low-molecular-weight heparins (LMWHs) have been shown to provide at least as good efficacy and safety outcomes as UFH regimens for prevention of these conditions. In addition to good efficacy outcomes with LMWHs compared with UFH, LMWHs have other advantages over UFH, including improved bioavailability, QD administration, more predictable anticoagulant response, lack of the need for monitoring, and suitability for outpatient use, thereby increasing convenience, reducing cost, and improving cost-to-benefit ratios. In carefully screened and managed patients, LMWH offers a cost-effective, convenient, and safe alternative to UFH for thrombosis management. The aim of this article is to summarize efficacy, safety, and pharmacoeconomic considerations when selecting LMWH versus UFH for thrombosis management in VTE and NSTE ACS.
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Heparin and heparin-derived drugs play a major therapeutic role in thrombotic and cardiovascular disorders.[1] Inpatient IV infusion of unfractionated heparin (UFH) followed by warfarin administration has traditionally been the standard pharmacologic therapy for the acute treatment of venous thromboembolism (VTE),[2,3] a term that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), and for non–ST-elevation (NSTE) acute coronary syndrome (ACS).[4] More recently, low-molecular-weight heparins (LMWHs) have been shown to provide at least as good efficacy and safety outcomes as UFH regimens for prevention and treatment of VTE[5–8] and NSTE ACS.[4,9,10] LMWHs have the additional advantages of ease of administration, predictability of anticoagulant response, lack of the need for monitoring, and suitability for outpatient use, thereby increasing convenience, reducing cost, and improving cost-to-benefit ratios.[5,11,12]

The American College of Chest Physicians (ACCP) provides strong evidence-based guidelines on VTE prevention that support use of either LMWH or UFH for most medical and surgical patients and VTE treatment that supports the use of LMWH over UFH in outpatient-

eligible patients.[13] The American College of Cardiology and the American Heart Association recommend that anticoagulation therapy with LMWH or UFH be added to antiplatelet therapy in patients with unstable angina or NSTE ACS.[14] This article summarizes efficacy, safety, and pharmacoeconomic considerations when selecting pharmacologic agents for thrombosis prevention and treatment in VTE and thrombosis management in NSTE ACS.

PHARMACOLOGIC THERAPY FOR PREVENTION OF VENOUS THROMBOEMBOLISM

Efficacy and Safety in Surgical Patients

Several studies have compared use of LMWH with UFH for prevention of thrombosis after major surgical interventions. In a meta-analysis of studies, Koch et al[6] analyzed data from 23 randomized, double-blind clinical trials comparing the effectiveness of LMWHs versus UFH for thrombosis prophylaxis after different types of major surgery. For patients undergoing general surgery, LMWHs and UFH were equally effective in preventing DVT, but low doses of LMWH were associated with reduced risk of wound hematoma ($P < 0.001$). For patients undergoing orthopedic surgery, LMWH was more effective than UFH, with lower rates of proximal DVT in patients receiving LMWH compared with UFH ($P = 0.002$).

KEY POINT

In patients undergoing general surgery, LMWHs and UFH were equally effective in preventing DVT, but low doses of LMWH were associated with reduced risk of wound hematoma.

In a study designed to evaluate risk factors for VTE in orthopedic patients, multivariate analyses identified the type of LMWH used as an independent predictor of VTE. Ten percent of patients receiving prophylaxis with enoxaparin experienced VTE, compared with 18% of patients receiving dalteparin (odds ratio for enoxaparin 0.4; 95% CI, 0.2–0.8; $P = 0.009$).[15] Authors theorize that this difference may reflect differences in anti-Xa activity between the 2 LMWHs, or differences in dosing, since enoxaparin was given BID and dalteparin QD.

Medical Patients and Bridging

Few studies have compared the effects of LMWHs versus UFH in patients with underlying medical diseases. A multicenter study of hospitalized patients with either severe respiratory disease or heart failure compared the safety and efficacy of the LMWH enoxaparin with UFH for prevention of VTE.[16] In the 451 patients evaluated, enoxaparin was at least as effective as UFH, with an incidence of VTE of 8.4% in patients receiving enoxaparin and 10.4% in patients receiving UFH. Enoxaparin was associated with similar death and bleeding rates but significantly fewer adverse events ($P = 0.044$)

Risk for thromboembolism is higher in patients with mechanical heart valves. Traditionally, inpatient bridging therapy with UFH has been used when these patients require discontinuation of anticoagulation therapy prior to elective or invasive procedures. Studies comparing the use of outpatient bridging therapy using LMWH versus inpatient bridging therapy using UFH for patients with mechanical heart valves shows outpatient LMWH therapy is as safe and effective as inpatient UFH therapy.[17,18] In addition, patients receiving bridging therapy with LMWH had shorter hospital stays and were less likely to undergo major surgery. In an integrated health maintenance organization based in Albuquerque, New Mexico, with approximately 200,000 members per year, use of the LMWH enoxaparin as bridge therapy in patients—including those with mechanical heart valves undergoing elective surgical procedures—resulted in a cost savings of approximately $212,475 per year from January 1998 to March 2002.[18]

PHARMACOLOGIC THERAPY FOR TREATMENT OF VENOUS THROMBOEMBOLISM

Efficacy and Safety

Several meta-analyses have analyzed the safety and efficacy of LMWHs compared with UFH in the treatment of DVT and VTE.[5–8,19,20] These meta-analyses collectively show LMWHs are at least as effective as or superior to UFH for prevention of recurrent VTE and reduction of overall mortality and major bleeding (**Table**).

TABLE. SUMMARY OF META-ANALYSES COMPARING THE EFFICACY AND SAFETY OF LOW-MOLECULAR-WEIGHT HEPARIN (LMWH) WITH UNFRACTIONATED HEPARIN FOR PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM (VTE)/DEEP VEIN THROMBOSIS (DVT).

Author	Number of Studies Included	Year Study Published	Types of LMWH Used	Main Efficacy Results with LMWH	Main Safety Results with LMWH
Treatment of VTE					
Siragusa et al[8]	13	1985–1993	Dalteparin (6) CY 222 (1) Fraxiparin (4) Logiparin (1) Enoxaparin (1)	Significant reduction in relative risk of recurrent VTE in blinded studies during first 15 days and over entire period	Significant reduction in relative risk of major bleeding in blinded studies Significant reduction in relative risk of overall mortality
Gould et al[20]	11	1991–1997	Nadroparin (4) Tinzaparin (1) Enoxaparin (2) Dalteparin (3) Reviparin (1)	No difference in prevention of thromboembolic recurrences	Significant reduction in odds ratio for major bleeding, but reduction in absolute risk not significant Significant reduction in mortality rates over 3 to 6 months
Rocha et al[5]	21	1985–1997	Dalteparin (8) CY 222 (1) OP 2123 (3) Certoparin (1) Nadroparin (4) Logiparin (1) Enoxaparin (2) Reviparin (1)	Significant improvement in clot reduction No difference in thromboembolic recurrences	Significant reduction in incidence of hemorrhage Significant decrease in total mortality
Dolovich et al[7]	13	1990–1997	Dalteparin (4) Nadroparin (4) Tinzaparin (2) Enoxaparin (2) Reviparin (1)	No difference in risk for recurrent VTE or PE	No difference in risk for major or minor bleeding or thrombocytopenia Significant reduction in risk of total mortality
Prevention of VTE					
Koch et al[6]	23	1986–1995	Dalteparin (11) Embolex (3) Mono-Embolex (4) Clivarin (2) Logiparin (1) Fraxiparin (1) Enoxaparin (1)	For general surgery, no difference in efficacy For orthopedic surgery, significant reductions in rates of proximal DVT and PE	For general surgery, significant reduction in wound hematoma with low-dose LMWH

PE = pulmonary embolism.

Two earlier meta-analyses noted benefits of LMWHs over UFH for the treatment of DVT and VTE.[8,19] Leizorovicz[19] analyzed the results of 20 randomized, controlled clinical studies comparing the safety and efficacy of LMWHs with UFH in patients with DVT. Significant reductions in overall mortality, major hemorrhage, and thrombus extension were observed in patients treated with LMWHs compared with UFH ($P < 0.05$). Recurrence of VTE was lower, though not significantly, in patients treated with LMWH. The authors concluded that LMWHs have a higher benefit-to-risk ratio compared with UFH for the treatment of VTE.

Siragusa et al[8] compared the effects of LMWHs and UFH on recurrent VTE and major bleeding in the treatment of acute VTE. The researchers analyzed data separately for studies that were or were not blinded. For blinded studies, the relative risk of recurrent VTE was significantly lower in patients treated with LMWHs compared with UFH over the first 15 days of treatment ($P < 0.05$) and over the entire period of anticoagulation therapy ($P < 0.01$). The relative risk of major bleeding was also significantly lower in patients treated with LMWHs compared with UFH in blinded studies ($P = 0.01$). More recent meta-analyses show potential benefits of LMWHs compared with UFH for treatment of DVT and VTE.[5,20] Gould et al[20] used clinical outcomes to compare the effects of LMWHs and UFH on major bleeding, recurrent thromboembolic events, and mortality rates over 3 to 6 months. Results again showed a significant reduction in the overall mortality rate with LMWHs compared with UFH ($P < 0.05$). The odds ratio suggested risk of major bleeding was lower in patients receiving LMWHs compared with UFH ($P < 0.05$), but the absolute risk reduction was not statistically significant. LMWH and UFH were equally effective in preventing thromboembolic recurrences.

Rocha et al[5] analyzed data from 4472 patients with DVT in 21 studies. Treatment with LMWHs was associated with improvement in clot venography ($P = 0.004$) and reductions in total mortality ($P = 0.012$) and incidence of hemorrhage ($P = 0.47$). No significant differences in recurrence of DVT were noted between groups. In this study, the effects of QD versus BID injections of LMWHs were also compared. QD dosing of LMWHs was associated with reduced risk of major bleeding ($P = 0.025$), whereas BID dosing was more effective for clot reduction ($P = 0.004$).

Another recent meta-analysis showed LMWHs were at least as effective as UFH for treatment of VTE.[7] In a meta-analysis of 13 randomized, blinded studies of patients with DVT treated with LMWHs or UFH, Dolovich et al[7] found no statistically significant differences between groups in risk of recurrent VTE, PE, major bleeding, minor bleeding, or thrombocytopenia. Total mortality risk, however, was significantly lower in patients treated with LMWHs compared with UFH (relative risk, 0.76; 95% CI, 0.59–0.98). Of the 13 studies included, 3 were considered to be outpatient trials. Comparison of inpatient and outpatient trials found a reduction in major bleeding in inpatient trials, highlighting the need for rigorous monitoring with outpatient treatment.

These meta-analyses included studies using different types of LMWH preparations. Because each LMWH has distinct anticoagulation effects,[1] results may have been different if only studies using 1 type of LMWH were included.

Outpatient Studies for the Treatment of DVT

The majority of studies comparing the efficacy and safety of LMWH with UFH for the treatment of VTE have been inpatient studies. The vast majority of patients with VTE are eligible for outpatient therapy with LMWH. Segal et al[21] summarized 8 studies that compared the efficacy, safety, and cost of outpatient use of a LMWH with inpatient use of UFH. All of the studies used enoxaparin, nadroparin, or dalteparin during intervention and follow-up. Results from a total of 3762 patients showed similar rates of recurrent DVT and major bleeding between groups, but shortened hospital stays and lower costs in individuals receiving LMWH as outpatients.

Not all patients are appropriate candidates for outpatient therapy with LMWH, and each patient must be individually assessed. Contraindications to outpatient therapy with LMWH include active bleeding, cardiopulmonary instability, hereditary bleeding disorders, history of heparin-induced thrombocytopenia, and allergy to heparin or LMWH.[2] Other potential contraindications that require clinical judgment include clinical factors such as gastrointestinal or genitourinary bleeding of recent onset, renal insufficiency, or socioeconomic/psychosocial factors such as potential nonadherence and geographic inaccessibility for follow-up care.[2,22]

KEY POINT

Many patients with VTE are appropriate candidates for outpatient therapy with LMWH, but each patient must be individually assessed.

Other Considerations and Pharmacoeconomic Evaluations

LMWH offers several advantages over UFH, including improved bioavailability, prolonged and predictable anticoagulant response, QD administration, lack of the need for monitoring, and convenience.[1] These advantages make LMWH suitable for outpatient use and translate into cost savings. In the description of outpatient studies by Segal et al,[21] use of LMWH was associated with shorter hospitalizations and lower costs. Median hospital stays were 2.7 days for patients receiving LMWH compared with 6.5 days for patients receiving UFH, resulting in a median cost savings of $1600 for patients receiving LMWH.

KEY POINT

In the analysis of outpatient studies by Segal et al, use of LMWH was associated with shorter hospitalizations and lower costs. Median hospital stays were 2.7 days for patients receiving LMWH compared with 6.5 days for patients receiving UFH, resulting in a median cost savings of $1600 for patients receiving LMWH.

A landmark Canadian study established the safety and efficacy of outpatient use of the LMWH enoxaparin compared with inpatient administration of UFH for treatment of DVT.[23] A later economic evaluation of this study compared the cost of treatment in a subset of 300 patients followed for up to 3 months.[24] Use of enoxaparin resulted in a cost savings of Can $3045. Spyropoulos et al[25] retrospectively replicated the Canadian study in a US managed care setting. They found no significant difference in the number of recurrent VTE or bleeding events, but again found substantial cost savings with outpatient enoxaparin administration compared with inpatient UFH administration. The mean cost savings per patient with enoxaparin was $2583.

KEY POINT

Antithrombin therapy is an integral part of managing NSTE ACS.

PHARMACOLOGIC THERAPY FOR NON–ST-ELEVATION ACUTE CORONARY SYNDROME

Antithrombin therapy is an integral part of managing NSTE ACS.[14] Several studies have shown that use of LMWH is at least as effective as or more effective than UFH in reducing the incidence of ischemic events.[4,9,10,26,27] The Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trial, a randomized, double-blind, placebo-controlled study of 3171 patients with NSTE ACS, showed that antithrombotic therapy with enoxaparin plus aspirin was more effective than therapy with UFH plus aspirin.[9] Risk of death, myocardial infarction (MI), or recurrent angina was significantly lower at 14 days ($P = 0.019$) and 30 days ($P = 0.016$). The need for revascularization was also significantly less at 30 days ($P = 0.001$). Rates of major bleeding did not differ significantly between groups.

A meta-analysis of data from the ESSENCE and Thrombolysis in Myocardial Infarction (TIMI 11B) trials found that enoxaparin was associated with a 20% reduction in death and serious cardiac ischemic events.[10] This reduction became apparent within the first few days of treatment and was still apparent after 43 days of treatment. Rates of minor bleeding were significantly higher in patients receiving enoxaparin ($P = 0.0001$), but no difference was found between groups in rates of major bleeding. Analysis of a subset of patients in the ESSENCE or TIMI 11B trials showed that obesity did not impact clinical outcomes of these trials.[23] Patients with severe renal impairment, however, had a higher risk

of clinical events and hemorrhage than patients without severe renal impairment.

The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and GlYcoprotein IIb/IIIa Inhibitors trial compared use of enoxaparin with UFH in high-risk patients with ACS.[27] Based on 6-month and 1-year follow-up data from 9978 patients in 487 hospitals in 12 countries, patients receiving enoxaparin or UFH had similar rates of death or MI. In patients receiving consistent therapy (only enoxaparin or UFH) during the hospitalization period, the reduction in rate of death or nonfatal MI that occurred within the first 30 days in patients receiving enoxaparin compared with UFH was maintained at 6 months ($P = 0.006$). One-year all-cause death rates in the 2 treatment groups and in patients receiving consistent therapy were similar.

In a recent review of 6 major trials that compared enoxaparin with UFH for the treatment of NSTE ACS (including the ESSENCE and TIMI 11B trials), results from ~22,000 patients showed the use of enoxaparin was associated with modest reductions in the incidence of the composite of death and MI at 30 days.[4] A larger effect was seen in patients who did not receive antithrombin pretreatment before randomization. No significant differences were found in rates of major bleeding or transfusions.

In addition to potential efficacy and safety advantages, LMWH offers other advantages over UFH for the prevention of ischemic events in NSTE ACS. Limitations of UFH include a high degree of protein binding, inactivation by platelet factor 4, a variable dose response, stimulation of platelet aggregation, and risk of heparin-induced thrombocytopenia.[4] In contrast, LMWHs have an effect higher in the coagulation cascade, with greater inhibition of factor Xa than IIa.[4]

Economic assessment of results from the ESSENCE trial showed cost savings with enoxaparin compared with UFH therapy.[12] Hospital billing data were available for 655 of the 936 US patients randomized to the ESSENCE trial. Total medical costs for the initial hospitalization were $763 less for patients receiving enoxaparin than for patients receiving UFH. At the end of 30 days, the total cost savings in patients receiving enoxaparin versus UFH was $1172.

CONCLUSIONS

LMWH is at least as effective as UFH for prevention of VTE events. In VTE treatment, compared with UFH, LMWH has been shown to reduce overall mortality and risk of major hemorrhage. For treatment of NSTE ACS, LMWH is associated with at least modest reductions in death and incidence of MI, with no increase in major bleeding. LMWH offers several advantages over UFH and yields cost savings in treatment of both VTE and NSTE ACS. In carefully screened and managed patients, LMWH offers a cost-effective, convenient, and safe alternative to UFH for thrombosis prevention and treatment.

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Dialogue Box

EDITORIAL BOARD

What patients with deep vein thrombosis would not be considered candidates for outpatient management with heparin?

SPYROPOULOS

Absolute contraindications would include high-risk patients with severe thrombocytopenia, active bleeding or a history of bleeding or at high risk of bleeding (ie, severe renal dysfunction), and patients with other comorbidities such as acute cardiopulmonary disease, as well as those with a history of heparin-induced thrombocytopenia, heparin sensitivity, and heparin allergy. Relative contraindications include age over 75 years, pregnancy, morbid obesity, and certain psychosocial and socioeconomic factors. The latter would include patients who are uncomfortable about outpatient initiation of therapy, language barrier issues, inability to access telephone or clinic, and home health service barriers. Over the past decade, it's been found that an increasing number of patients with some of these relative contraindications can be safely managed in the outpatient arena. As a result, I would estimate that 75% to 80% of patients with venous thromboembolism (VTE) would be regarded as good candidates for outpatient treatment. It's only a small minority of patients who would not be outpatient candidates, thanks to the growing sophistication of anticoagulant home management services.

EDITORIAL BOARD

Are the same benefits described in the analysis by Segal et al for low-molecular-weight heparin (LMWH) achievable with unfractionated heparin (UFH)?

SPYROPOULOS

You bring up a very good point because some recent studies by Clive Kearon and others have shown at least the theoretic feasibility of outpatient treatment with adjusted-dose subcutaneous UFH. The only trouble is on the operational side. The need for monitoring and frequent laboratory testing, along with safety concerns such as heparin-induced thrombocytopenia (HIT) and major bleeding, combine to make UFH the less attractive option. LMWH is really the drug of choice for outpatient treatment because of the ease of administration, the predictable pharmacokinetic characteristics, and the lack of a need for monitoring. We now have 10 years' worth of data that demonstrate excellent clinical outcomes with the use of LMWH, not only in randomized controlled trial settings but also in routine clinic settings, provided the proper system is in place.

EDITORIAL BOARD

Please elaborate more on the pharmacokinetic advantages offered by LMWH over UFH.

SPYROPOULOS

UFH, having a large glycosaminoglycan side chain, possesses a high propensity for binding to plasma proteins, endothelial cells, macrophages, hepatocytes, and other cell types. As a result, UFH is associated with both interindividual and intraindividual variability and thus requires frequent monitoring. LMWH, on the other hand, produces a more predictable anticoagulant response, which is a reflection of its better bioavailability, longer half-life, and dose-independent clearance. These properties result in a more predictable anticoagulant response and preclude the need for laboratory monitoring. In addition, LMWH is associated with a lower risk of HIT; for LMWH the risk of HIT is 0.3% to 0.5%, whereas the risk of HIT is in the order of about 2% to 5% with UFH.

EDITORIAL BOARD

Isn't LMWH also associated with a lower risk of osteoporosis?

SPYROPOULOS

Absolutely. There are studies that show in a high-risk patient cohort group (such as during pregnancy or the elderly female), radiographic evidence of osteopenia develops in as many as 30% of patients on UFH versus 3% to 4% in patients treated with LMWH.

Dialogue Box

EDITORIAL BOARD

Are there any circumstances where UFH would be favored over LMWH?

SPYROPOULOS

Yes, in the patient with a very high bleeding risk or recent bleeding, as well as in the patient facing an imminent surgical procedure. One of the key advantages of UFH is the fact it has a very short half-life (on the order of about 60 minutes depending on what moiety of UFH is used), whereas LMWH has a half-life on the order of about 4 to 6 hours. The fact that you can shut off UFH therapy very quickly, as well as the fact that you can reverse it 100% with protamine, makes it the preferred agent in patients in whom the need for rapid reversal is more likely to arise.

EDITORIAL BOARD

The analysis conducted by Rocha and associates seemed to demonstrate that twice-daily dosing with LMWH is more effective for clot reduction than once-daily dosing. Is twice-daily dosing favored for treating patients with VTE?

SPYROPOULOS

Not necessarily. For most patients, I'm still very comfortable with once-daily dosing. Patients in whom twice-daily dosing may be preferred are high-risk patients, such as morbidly obese patients with a body mass index of >35 kg/m^2, patients with very borderline kidney function, pregnant patients, or patients with cancer or large clot burden (ie, ileofemoral thrombosis). These patients, however, represent only about 5% to 10% of your total patient population.

EDITORIAL BOARD

Do you think that LMWH and UFH are comparable with regard to outcomes and that the major difference is with respect to ease of administration?

SPYROPOULOS

Yes, that's exactly right. If UFH is used in a clinical trial setting, most of the data support that there's essentially equal efficacy and safety between both agents. However, because of its large molecular size and nonspecific binding, what happens is that even with the best intentions, even following a Raschke-type weight-based nomogram, only 30% of patients treated with UFH actually reach and maintain the desired therapeutic range. I think what we're dealing with is really the mechanics or the operational issues associated with the drug. This becomes an even greater issue if you give it subcutaneously where there's even greater variability.

EDITORIAL BOARD

What are your thoughts regarding the use of LMWH in the treatment of pulmonary emboli?

SPYROPOULOS

Extensive data from trials in the mid-1990s demonstrate for patients with primary pulmonary embolism (PE) as the index VTE event, there's equal safety and efficacy using LMWH. The recently published Matisse study compared fondaparinux and enoxaparin for PE treatment and found almost identical safety and efficacy profiles for those agents. Other data, such as the Wells data looking at PE outcomes using enoxaparin in a routine clinic setting, show excellent clinical outcomes using enoxaparin. Suffice it to say that strong data now exist that favor the use of LMWH for PE treatment, either in the inpatient or outpatient setting.

EDITORIAL BOARD

How do you decide which patient with a PE can be safely treated as an outpatient?

SPYROPOULOS

Although this has not been validated in terms of large-scale data, I base my decision on a risk stratification scheme, looking for evidence of right ventricular dysfunction, dilatation, and elevated pulmonary artery pressures. To assess these parameters, I order a transthoracic echocardiogram. If that echocardiogram shows normal chamber size and the patient has no evidence of hemodynamic instability and no evidence of

Dialogue Box

right ventricular dysfunction, I'm very comfortable with starting treatment or continued treatment in the outpatient setting. The majority of those patients will get at least a 24-hour observational period in the hospital so we can facilitate exams and watch the patient in a controlled setting. In centers in Canada, outpatient PE treatment is now becoming the standard of care.

EDITORIAL BOARD

In patients adequately anticoagulated on a continuous heparin infusion, how would you convert them to LMWH?

SPYROPOULOS

One would simply stop the infusion and then, after 4 to 6 hours, start the LMWH at its prespecified dosing scheme.

EDITORIAL BOARD

Is it true that in terms of timing, you have a 6-hour window following surgery to initiate prophylactic therapy?

SPYROPOULOS

Yes. Russell Hull has advocated a "just-in-time" dose of using anticoagulants whether it be with UFH or LMWH. I think that we've all surmised, the closer you give that first dose postoperatively, the greater the efficacy but at the expense of greater bleeding. As a result, for most surgical procedures that just-in-time dose is now moved outwards toward 8 to 12 hours instead. What we're seeing in the United States is that many surgeons like to give that first dose at 12 hours, if not later.

EDITORIAL BOARD

In a patient with a history of HIT associated with UFH use, is LMWH also contraindicated?

SPYROPOULOS

Absolutely. There's a greater than 80% cross-reactivity with any type of heparin. So any type of heparin (including LMWH) would be contraindicated. In such patients, alternative options would include lepirudin, argatroban, and possibly fondaparinux.

EDITORIAL BOARD

What about for patients with a history of thrombocytopenia unrelated to heparin use?

SPYROPOULOS

If it's severe, such as a platelet count under 100,000, I would use fondaparinux. If the platelet counts are over 100,000, without documented HIT, I'm comfortable with the LMWHs.

Prevention of Thrombosis with Warfarin, Aspirin, and Mechanical Methods

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Venous thromboembolism (VTE) is a serious disorder and a major cause of morbidity and mortality among acutely ill medical patients. However, despite the growing number of patients with acute medical illnesses who have an associated risk of VTE, the widespread use of VTE prophylaxis does not yet occur for both surgical and nonsurgical patients. Although individuals at greatest risk for VTE include patients undergoing major orthopedic surgery and those with medical conditions that require prolonged immobilization, all patients who have acute medical illnesses should be considered for VTE prophylaxis. Several strategies, including various mechanical and pharmacologic approaches, are currently used for VTE prophylaxis. Increased awareness about the full range of options for VTE prophylaxis can help health care providers select the appropriate course of action to help reduce the incidence of VTE among patients with acute medical illnesses. (*Clinical Cornerstone.* 2005;7[4]:49–56)

Two million people each year are affected by venous thromboembolism (VTE) in the United States, making it the third most common cardiovascular disease after coronary heart disease and stroke.[1] VTE includes the development of deep vein thrombosis (DVT) and pulmonary embolism (PE); of the estimated 600,000 Americans each year who develop PE, 60,000 people will die of this complication.[2] DVT and PE can develop spontaneously, or they can result from medical circumstances such as surgery, prolonged bed rest, or trauma. Several strategies, including mechanical and pharmacologic approaches, are currently available for VTE prophylaxis (**Table I**).[3]

Recently, several new anticoagulants have been evaluated in Phase III trials. The THRombin Inhibitor in Venous thromboEmbolism (THRIVE) Treatment Study, for example, found that the oral direct thrombin inhibitor (DTI) ximelagatran was as effective as standard enoxaparin/warfarin treatment for the prevention of recurrent VTE.[4] In this study of 2489 patients with acute DVT (of which one third had concomitant PE), VTE recurred in 26 of the 1240 patients assigned to receive 6 months of treatment with ximelagatran (estimated cumulative risk, 2.1%) and in 24 of the 1249 patients assigned to receive 6 months of treatment with enoxaparin/warfarin (estimated cumulative risk, 2.0%).

Another randomized trial evaluated the efficacy and safety profile of the low-molecular-weight heparin (LMWH) fondaparinux compared with the LMWH enoxaparin followed by warfarin in patients with acute DVT.[5] At 3 months, symptomatic VTE had recurred in 3.9% of patients who had received fondaparinux and in 4.9% of patients who had received enoxaparin and warfarin, demonstrating the noninferiority of fondaparinux in these patients. Major bleeding was recorded in about 1% of the patients in both groups. Several other studies are now under way to assess newer agents indicated for the prevention of VTE.

Currently, the use of an LMWH followed by a vitamin K antagonist, such as warfarin, for up to 6 months is appropriate for use in preventing thrombus formation and embolism in most patients[6]; however, some patients, such as those at risk for heparin-induced thrombocytopenia or excessive bleeding, may benefit from other approaches. These alternative strategies are addressed in the current discussion.

TABLE I. MECHANICAL AND PHARMACOLOGIC PREVENTATIVE MEASURES FOR VENOUS THROMBOEMBOLISM (VTE).

Practice	Type	Description	Comment
Graduated elastic stockings	Mechanical	Fitted hose that extend above the knee	Fitted hose are more efficacious than nonfitted
Intermittent pneumatic compression	Mechanical	Devices fitted over lower extremities that sequentially inflate and deflate	
Aspirin	Pharmacologic	Usually 325 mg/d	
Warfarin	Pharmacologic	5–10 mg started the day of or after surgery; adjust to achieve an INR of 2–3	Monitoring of INR needed
Low-dose unfractionated heparin	Pharmacologic	Generally 5000 U SC BID or TID, though some studies have adjusted dose to maintain partial thromboplastin time at high end of normal	Contraindicated if active bleeding or history of thrombocytopenia; no need to follow coagulation studies (unless adjusted dose is used)
Low-molecular-weight heparin	Pharmacologic	Dose depends on agent used, type of surgery, and VTE risk	No need to monitor coagulation studies
DTI	Pharmacologic	Dose depends on agent used, type of surgery, and VTE risk	DTI pharmacodynamics are monitored by the aPTT, with a target aPTT ratio from 1.5–2.5 or 3.0

INR = international normalized ratio; DTI = direct thrombin inhibitor; aPTT = activated partial thromboplastin time.
Adapted with permission.[3]

WARFARIN FOR THROMBOPROPHYLAXIS

Warfarin has been a cornerstone of oral anticoagulant therapy for more than 50 years. It has been used to prevent DVT and PE; its effectiveness has been clearly established in randomized clinical trials.[7] Warfarin also is indicated for the prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, for the primary prevention of acute myocardial infarction in high-risk patients, and for the prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction.[8]

Warfarin can be used for long-term thromboprophylaxis, due to convenient oral administration and its low cost. However, warfarin is difficult to use for many reasons. These include variability in dose response (the patient's international normalized ratio [INR] must be monitored regularly when using this agent [**Table IIA** and **Table IIB**]),[9] a narrow therapeutic window, the potential for interaction with other drugs (**Table III**),[10] and standardization issues.

American College of Chest Physicians (ACCP) guidelines issued in 2004 regarding the use of warfarin and other vitamin K antagonists for anticoagulation carry recommendations with a status of Grade 2B or 2C, meaning that the benefit-to-risk ratio is not clear-cut for all patients and that the supportive evidence comes from randomized clinical trials with inconsistent results or methodologic weaknesses or from observational studies.[8] Current recommendations indicate that vitamin K antagonists should be started at doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the patient's

KEY POINT

Current recommendations indicate that vitamin K antagonists should be started at doses between 5 and 10 mg for the first 1 or 2 days for most individuals, with subsequent dosing based on the patient's INR response.

TABLE IIA. WARFARIN STARTING DOSE.

Patient Group	Recommendations	Grade
Most patients	• 5–10 mg QD for the first 1–2 days • Thereafter, adjust by INR	2B
Patients >60 years old	• ≤5 mg QD to start • Thereafter, adjust by INR	2C
Patients who: • are debilitated • are undernourished • have liver disease • have congestive heart failure	• ≤5 mg QD to start • Thereafter, adjust by INR	2C

The guidelines recommend the following monitoring frequency for patients in the community:

- Start INR monitoring after the first 2–3 doses (Grade 2C)
- Monitor INR every few days until stable (at least 2 consecutive INRs stable)
- Then, decrease frequency of monitoring gradually, using clinical judgment; interval between INRs should not be longer than 4 weeks (Grade 2C)

INR = international normalized ratio.
Adapted with permission.[9]

TABLE IIB. WARFARIN DOSAGE ADJUSTMENT WHEN THE INTERNATIONAL NORMALIZED RATIO (INR) IS ELEVATED.

INR	Recommendations	Grade
Above therapeutic range but <5.0	• Skip a dose (or lower the dose) and monitor more frequently. Start at a lower dose when INR therapeutic. • If minimally above therapeutic range, no dose adjustments may be needed.	2C
INR ≥5.0 and <9.0 no significant bleeding	• Skip the next 1–2 doses, monitor more frequently, and start at a lower dose when INR therapeutic. • Or, skip the next dose and give vitamin K (≤5 mg orally for rapid reversal). This will lower the INR within 24 hours. If the INR is still high, give an additional 1–2 mg of vitamin K orally. Start warfarin at a lower dose when INR therapeutic.	2C
INR ≥9.0 no significant bleeding	• Hold warfarin and give vitamin K (5–10 mg orally). This will lower the INR within 24–48 hours. If the INR is still high, give additional vitamin K orally. Start warfarin at a lower dose when INR therapeutic.	2C
INR any value above therapeutic range, serious bleeding	• Hold warfarin and give vitamin K (10 mg by slow IV infusion). Vitamin K can be repeated every 12 hours. May also give fresh plasma and prothrombin complex concentrate (or recombinant factor VIIa).	1C
Life-threatening bleeding	• Hold warfarin and give prothrombin complex concentrate and vitamin K (10 mg by slow IV infusion).	1C

Note: INR values >4.5 are less reliable than values closer to the therapeutic range, so these recommendations are an approximate guide. When warfarin therapy is started or changed, frequent INR monitoring is needed (up to twice weekly).
Adapted with permission.[9]

TABLE III. DRUGS THAT ALTER RESPONSE TO WARFARIN.

Increase INR		Decrease INR
Phenytoin*	Amiodarone†	Phenobarbital†
Metronidazole†	Cimetidine†	Rifampin/rifabutin†
Fluconazole†	Erythromycin†	Carbamazepine*
Itraconazole†	Dong quai*	Vitamin K†
Ketoconazole†	Statins*	Phenytoin* (chronic use)
Sulfamethoxazole/ trimethoprim†	Alcohol‡	Sucralfate*
		Ginseng*
		Alcohol‡

INR = international normalized ratio.
*Moderate interaction.
†Severe interaction.
‡Effect of alcohol on INR is unpredictable, may increase/decrease INR. For a detailed review, see Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med.* 2005;165:1095–1106.
Adapted with permission.[10]
Note: This list is not all-inclusive; each patient's INR should be monitored after initiating or modifying any drug therapy.

INR response (**Table IV**).[11] An INR of 2.0 to 3.0, which is considered moderate or standard intensity, remains the target range for most patients needing therapy with a vitamin K antagonist.[8]

Since the most common complication of warfarin therapy is bleeding, studies have evaluated whether a lower-intensity dose of warfarin is as effective and safe as a conventional-intensity dose. One recent analysis evaluated 738 patients who were randomly assigned to continue warfarin therapy with a target INR of 2.0 to 3.0 (conventional intensity) or a target INR of 1.5 to 1.9 (low intensity). Patients were followed for an average of 2.4 years. Researchers found that conventional-intensity warfarin therapy was more effective than low-intensity warfarin therapy and that using a lower dose did not reduce the risk of clinically important bleeding.[12] Furthermore, major bleeding episodes were reported in 9 patients in the low-dose group and 8 patients in the conventional group.

Long-term low-intensity warfarin (target INR, 1.5–2.0) has been found in clinical studies to be effective in preventing recurrent VTE.[13] Ridker et al[13] randomized 508 patients with idiopathic VTE who had received full-dose anticoagulation therapy to receive placebo or low-intensity warfarin. Patients were followed for a median of 6.5 months, monitored for recurrent VTE, major hemorrhage, and death. Of the 253 patients in the placebo group, 37 had recurrent VTE compared with 14 of 255 patients receiving warfarin, indicating a risk reduction of 64% with warfarin treatment (hazard ratio, 0.36 [95% CI, 0.19–0.67]; $P < 0.001$). Low-intensity warfarin was associated with a 48% reduction in a composite end point of recurrent VTE, major hemorrhage, and death, compared with placebo. In addition, the number of occurrences of major hemorrhage (5 of 255 patients in the low-intensity warfarin groups vs 2 of 253 patients in the placebo group; $P = 0.25$) and death (4 of 255 patients vs 8 of 253 patients, respectively; $P = 0.26$) was not significantly different when comparing low-intensity warfarin and placebo.[13]

Warfarin will likely remain an important agent for the prevention of VTE, providing several benefits such as low cost and ease of administration. However, further studies of warfarin in combination with LMWHs and DTIs are clearly warranted.

ASPIRIN FOR THROMBOPROPHYLAXIS

Although aspirin is an antiplatelet agent that can help prevent blood from clotting inside the blood vessels,[14,15] aspirin alone is not recommended for thromboprophylaxis for several reasons. First, studies supporting the use of antiplatelet drugs for VTE are limited. Second, numerous trials have found a lack of benefit or inferior results with aspirin therapy.[16,17] In addition, aspirin therapy increases the risk of major bleeding, especially when combined with other agents.[7]

The Pulmonary Embolism Prevention trial—a randomized placebo-controlled trial of 13,356 patients undergoing surgery for hip fracture in hospitals located in Australia, New Zealand, South Africa, Sweden, and the United Kingdom—found that low-dose aspirin reduces the risk of PE (including fatal events) and symptomatic DVT.[15] Patients received 160 mg/d of aspirin or placebo starting before surgery and continued treatment for 35 days, receiving

KEY POINT

Although aspirin is an antiplatelet agent that can help prevent blood from clotting inside the blood vessels, aspirin alone is not recommended for thromboprophylaxis.

TABLE IV. SUGGESTED TREATMENT STRATEGIES FOR VARIOUS INTERNATIONAL NORMALIZED RATIO (INR) VALUES IN PATIENTS RECEIVING WARFARIN ADMINISTERED TO ACHIEVE A TARGET INR OF 2.0 TO 3.0.

INR Value	Clinical Data	Treatment Strategy
Any elevation	Life-threatening bleeding	1. Withhold warfarin. 2. Replace coagulation factors using plasma or complex concentrates. 3. Administer IV vitamin K (5–10 mg, with the dose depending on the INR). 4. Correct mechanical causes of hemorrhage. 5. Provide medical support, including transfusion, as required.
Any elevation	Major (non–life-threatening bleeding)	1. Withhold warfarin. 2. Consider administration of plasma or complex concentrates. 3. Administer IV vitamin K (1–10 mg, with the dose depending on the INR). 4. Correct mechanical causes of hemorrhage. 5. Provide medical support, including transfusion, as required.
4.5–6.0	No bleeding	1. Withhold warfarin and recheck INR in 24–48 hours OR 1. Withhold warfarin, administer 1 mg oral vitamin K and recheck INR in 24–48 hours OR 1. Reduce warfarin dose, recheck INR in 24–48 hours.
6.1–10.0	No bleeding	1. Withhold warfarin and recheck INR in 24 hours OR 1. Withhold warfarin, administer 1 mg oral vitamin K and recheck INR in 24 hours OR 1. Withhold warfarin, administer 1–2.5 mg of oral vitamin K, consider using plasma or complex concentrates ONLY IN PATIENTS AT HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours.
10.1 and above	No bleeding	1. Withhold warfarin, administer 1–5 mg of oral vitamin K and recheck INR in 24 hours OR 1. Withhold warfarin, administer 0.5–1.0 mg of IV vitamin K and recheck INR in 24 hours OR 1. Withhold warfarin, administer 1–5 mg of oral vitamin K, consider using plasma or complex concentrates ONLY IN PATIENTS AT HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours OR 1. Withhold warfarin, administer 0.5–1.0 mg of IV vitamin K, consider plasma or complex concentrates ONLY IN PATIENTS WITH HIGH RISK OF HEMORRHAGE and recheck INR in 24 hours.

Note: For patients receiving warfarin with a higher target INR, the ranges presented should be adjusted upward. In all cases, the cause of the excessive prolongation of the INR should be sought and corrected.
Adapted with permission.[11]

additional thromboprophylaxis as needed. Among patients with hip fracture taking aspirin, risk of PE was reduced by 43% (95% CI, 18–60; $P = 0.002$) and symptomatic DVT was reduced by 29% (95% CI, 3–48; $P = 0.03$), compared with placebo. No increase in death rate was observed in the aspirin group, although the number of postoperative transfused bleeding episodes was higher in the group taking aspirin ($P = 0.04$).[15]

LMWH was found to be more effective than aspirin in high-risk subjects, according to the findings of the LONFLIT3 study that evaluated methods of DVT prevention in high-risk subjects after long (>10 hours) airplane flights.[18] A total of 300 participants at high risk for DVT were randomized into 3 groups: 1 group received no treatment; 1 group received 400 mg of oral, soluble aspirin QD for 3 days (starting 12 hours before the beginning of the flight); or 1 group received 1 weight-adjusted dose of the LMWH enoxaparin, injected 2 to 4 hours before the flight. The incidence of DVT was 4.82% in the control group and 3.6% in the aspirin group; in the LMWH group, 0.6% of patients experienced thrombotic events ($P < 0.002$ compared with the other 2 groups).

Mild gastrointestinal symptoms were reported in 13% of the patients who received aspirin therapy.

MECHANICAL METHODS FOR VTE PROPHYLAXIS

Mechanical methods of thromboprophylaxis are intended to increase venous outflow from the legs and/or reduce blood stasis within leg veins and are attractive primarily due to the absence of bleeding risk compared with pharmacologic agents. As a result, these methods are particularly useful for patients at high risk of bleeding. They are also suitable for chronically bedridden patients, in whom prolonged therapy with heparins may be problematic due to bleeding risk or osteoporosis. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy recommends mechanical prophylaxis in case of contraindication to anticoagulant therapy in nonsurgical patients.[19]

Efficacy studies comparing the use of mechanical prophylaxis (such as graduated compression socks, pneumatic compression devices, and venous foot pumps) versus the use of pharmacologic anticoagulation approaches in nonsurgical patients are lacking to date.[20] However, mechanical prophylaxis is often used with anticoagulation therapy to improve effectiveness.[21,22] Several studies have shown that the use of compression socks or elastic stockings is advantageous in patients with myocardial infarction[23] or in reducing DVT following acute stroke.[24]

KEY POINT

Mechanical prophylaxis is often used with anticoagulation therapy to improve effectiveness.

A study that analyzed the outcomes of a total of 1892 patients who were treated with intermittent pneumatic compression following gynecologic surgery found that patients who were most likely to fail intermittent pneumatic compression prophylaxis included those patients with cancer, patients with a history of DVT, and patients at age ≥60 years.[25] Researchers concluded that patients with more than 1 of these independent risk factors should be considered for more intense prophylaxis regimens.[25]

The effectiveness and safety of mechanical versus LMWH approaches for DVT prophylaxis have been compared in patients after total hip replacement.[26] A total of 216 patients were randomized for DVT prophylaxis management with either the use of a foot pump or LMWH, resulting in 200 patients available for analysis (16 patients were excluded because they either did not tolerate the continuous use of the foot pump or the use of LMWH). DVT was detected by serial duplex sonography in 3 of 100 patients in the foot-pump group and in 6 of 100 patients in the LMWH group ($P < 0.05$). In addition, the mean postoperative drainage was lower in the foot-pump group (259 mL vs 328 mL; $P < 0.05$), and they had less swelling of the thigh (10 mm compared with 15 mm; $P < 0.05$). Researchers concluded that mechanical prophylaxis of DVT after total hip replacement was effective and safe.[26]

The issue of adequate patient compliance with mechanical devices warrants consideration; some patients find these methods difficult to tolerate. For example, a study by Westrich and Sculco[16] showed that the degree of compliance among 122 patients who experienced total knee arthroplasty was associated with the prevalence of DVT after surgery—no DVT was present in patients with an average of 80% compliance with the use of pneumatic plantar compression, but a significant incidence of DVT was observed in patients averaging 55% compliance.

A study by Robertson et al[27] evaluated a consecutive series of patients undergoing total joint arthroplasty who were sequentially treated with 2 mechanical devices designed to prevent DVT. One group of 104 patients wore a thigh-high sequential compression device. The second group of 120 patients wore a foot pump. As measured by responses to a questionnaire, patient satisfaction among patients using the foot pump was significantly higher than for those using the sequential compression device (73% vs 55%, respectively). The study also found a higher degree of compliance among patients using the foot pumps as compared with patients using the sequential compression device.[27]

Filter placement within the inferior vena cava (IVC) can be an effective intervention for VTE prophylaxis in certain patients. Although IVC filters do not prevent DVT, they can prevent PE.[28] Two recent studies (a study of 94 patients with multiple trauma who underwent placement of temporary IVC filters in 2002/2003 and another study of 88 multiple-trauma patients who received temporary IVC filter placement at the intensive care unit bedside from 2002 to 2004) found that this

approach was simple and safe, prevented fatal PE, and served as an effective bridge to anticoagulation therapy until other VTE prophylaxis measures could be taken.[28,29]

A decision to use IVC filters is based on several considerations, including the patient's clinical condition, the type of filter available, the alternative access sites available, and the expertise of the physician.[30] Approximately 30,000 to 40,000 IVC filters are placed in patients each year in the United States, particularly in about 50% of trauma patients.[31] IVC filters are often considered when a clear contraindication to anticoagulant therapy exists or when VTE occurs despite adequate anticoagulation.[31] However, vena cava interruption is often regarded as an incomplete treatment for VTE because, unlike anticoagulant therapy, it offers no beneficial effect on the prevention of DVT or the prevention of DVT extension, recurrence, and subsequent postthrombotic syndrome.[32] Therefore, physicians recommend the use of IVC filters selectively in patients with contraindications to anticoagulants or those with recurrent PE despite adequate anticoagulation. Whenever possible, pharmacologic anticoagulation is the preferred approach to VTE prophylaxis in patients at risk for VTE.

KEY POINT

IVC filters are often considered when a clear contraindication to anticoagulant therapy exists or when VTE occurs despite adequate anticoagulation.

CONCLUSIONS

The use of VTE prophylaxis is justified by the often clinically silent presentation of VTE and its high prevalence among hospitalized patients. VTE is diagnosed in ~170,000 incident cases among hospitalized patients in the United States each year; >20,000 patients die of VTE before discharge.[33] VTE prophylaxis is clearly the most cost-effective strategy for managing DVT and PE.[34] At greatest risk are patients undergoing major orthopedic surgery and those with medical conditions that require immobilization for 5 days or longer. Strategies currently used to prevent VTE include anticoagulant therapy with heparin (LMWH or unfractionated heparin), DTIs, oral anticoagulants such as warfarin, and mechanical methods. For patients undergoing total hip or knee replacement, treatment with adjusted-dose warfarin, LMWH, or fondaparinux may be used. Warfarin has been the leading oral anticoagulant agent for various thromboembolic events. The DTI ximelagatran—the first clinically tested oral anticoagulant since the introduction of warfarin in the early 1940s—is currently being evaluated for use in the United States for the prevention and treatment of VTE.

KEY POINT

VTE prophylaxis is clearly the most cost-effective strategy for managing DVT and PE.

Several randomized clinical trials have evaluated the efficacy of pharmacologic prophylaxis, with only a limited number of studies that have assessed the efficacy of mechanical prophylaxis. More studies are needed to assess various approaches to achieve maximal prevention of VTE.

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Commentary on Current Literature

Richard A. Johnson, MD

Preventing Venous Thromboembolism in Medical Patients
Leizorovicz A, Mismetti P.
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Given the increased number of patients hospitalized for acute medical illnesses and the associated risk of venous thromboembolism (VTE), the use of prophylaxis has become a public health matter. Thromboprophylaxis is not widely practiced in acutely ill medical patients, due in part to the heterogeneity of this group and the perceived difficulty in assessing those who would most benefit from treatment. Nevertheless, the results of recent well-conducted clinical trials support the evidence-based recommendations for more widespread systematic use of low-dose low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) in this population. Three large well-controlled studies (MEDENOX, PREVENT, and ARTEMIS) in acutely ill medical patients confirm previous findings that different at-risk patient populations show a consistent 50% reduction in VTE events with LMWH and fondaparinux. A meta-analysis in nearly 5000 patients in internal medicine comparing UFH and LMWH revealed a trend for reduction of deep vein thrombosis and pulmonary embolism with LMWH. Based on duration of use in clinical trials in acutely ill medical patients, prophylactic treatment with UFH and LMWH is recommended for 2 weeks.

COMMENTARY

This paper by Leizorovicz and Mismetti provides a comprehensive review of recent clinical trials and evidence-based recommendations regarding the use of VTE prophylaxis for patients with acute illnesses. Of the approximately 300,000 cases of VTE now estimated to develop each year in the United States, about 75% of these VTE cases occur in acutely ill nonsurgical patients. However, despite an ever-growing population of patients with acute medical illness who have an associated risk of VTE, the widespread use of VTE prophylaxis does not yet occur in various groups of at-risk patients. Reasons for this limited use of VTE prophylaxis include lack of awareness of the risk of VTE in certain groups of patients; concern about bleeding; uncertain cost-to-benefit ratio, and lack of convenient risk-stratification tools for identifying those patients who can benefit from VTE prophylaxis. The findings of 3 large, placebo-controlled studies—MEDENOX, PREVENT, and ARTEMIS—found a reduction of VTE in the range of 50% with the use of LMWH and fondaparinux for a maximum of 14 days, with a minimal risk of major bleeding. More widespread and systematic use of VTE prophylaxis can greatly reduce the risk of VTE in patients with acute medical illnesses.

Commentary on Current Literature

Richard A. Johnson, MD

Retrospective Database Analysis of the Prevention of Venous Thromboembolism with Low-Molecular-Weight Heparin in Acutely Ill Medical Inpatients in Community Practice

McGarry LJ, Thompson D.
Clin Ther. 2004;26:419–430.

BACKGROUND: Clinical trials have demonstrated that prophylaxis with low-molecular-weight heparin reduces the occurrence of venous thromboembolism (VTE) among acutely ill medical inpatients in the experimental setting.

OBJECTIVE: The goal of this retrospective database analysis was to examine the outcomes of low-molecular-weight heparin thromboprophylaxis among acutely ill medical inpatients in community practice.

METHODS: Using a large, geographically diverse, multihospital US database, we identified persons aged ≥40 years who had a hospital stay ≥6 days for an acute medical condition (including selected circulatory disorders, respiratory disorders, infectious diseases, or neoplasms) during calendar-year 2000. From these patients, those who received either enoxaparin thromboprophylaxis or no thromboprophylaxis were identified. Surgical patients, patients with nonthrombotic conditions requiring anticoagulant therapy, those transferred from or discharged to another acute care facility, and those medically ineligible for anticoagulation therapy were excluded. We compared the incidence of deep-vein thrombosis (DVT), pulmonary embolism (PE), all VTE (ie, DVT and/or PE), and death during the hospital stay in the 2 cohorts.

RESULTS: A total of 162 patients receiving enoxaparin thromboprophylaxis and 3557 receiving no thromboprophylaxis were identified. The risk of VTE over the course of hospitalization was 1.9% with enoxaparin thromboprophylaxis versus 6.2% with no thromboprophylaxis (relative risk = 0.30; $P = 0.023$); mortality was similar in the 2 groups (8.0% vs 7.3; P = NS).

CONCLUSIONS: Using hospital administrative data, we observed a 70% lower risk of VTE for hospitalized acutely ill medical patients receiving low-molecular-weight heparin thromboprophylaxis versus those receiving no thromboprophylaxis; these results are consistent with findings from clinical trials of low-molecular-weight heparin versus placebo. We conclude that the low-molecular-weight heparin enoxaparin is effective in reducing the risk of VTE in acutely ill medical inpatients in community practice.

COMMENTARY

This analysis by McGarry and Thompson highlights the need to focus more attention on VTE prophylaxis among acutely ill medical patients in community practice. In addition to surgical patients at elevated risk for VTE, nonsurgical patients who are hospitalized for various conditions (including congestive heart failure, chronic obstructive pulmonary disease, acute infections, or cancer) often have prolonged lengths of stay with periods of immobility, placing them at increased risk of VTE. This analysis of administrative data from 23 acute care institutions throughout the United States for calendar-year 2000 examined the outcomes of 2 groups of patients (1 group of 162 patients who received enoxaparin thromboprophylaxis and 1 group of 3557 patients who received no thromboprophylaxis). Researchers observed a 70% lower risk of VTE among patients receiving enoxaparin thromboprophylaxis as compared with patients who received no thromboprophylaxis. In community practice, many patients with acute illnesses who can potentially benefit from thromboprophylaxis are not receiving this care. Health care professionals are encouraged to identify risk factors for VTE (including a history of VTE, advanced age, obesity, varicose veins, and estrogen use) in all patients and adopt a more proactive approach to help prevent VTE.