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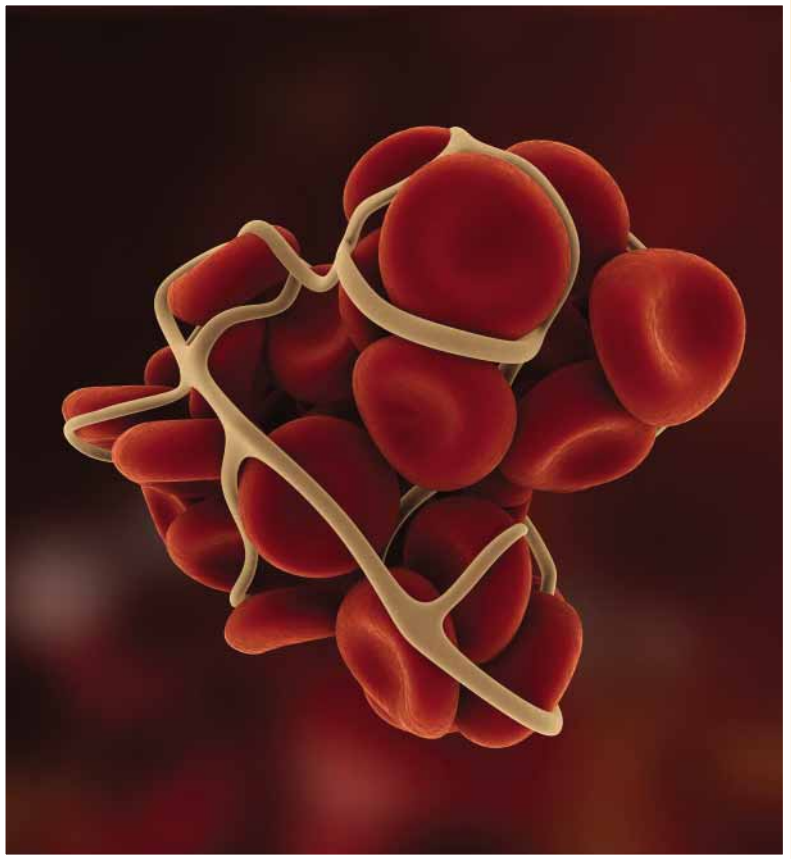
Prevention of Venous Thromboembolism in Hospitalized Medical Patients

Clinical Questions: Test Yourself

Prevention of VTE in Hospitalized Medical Patients: Just Do It!

Prevention of VTE in Medical Patients: Current Evidence and Recommendations



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PROGRAM DESCRIPTION

This CME activity consists of a print monograph with three sections: (1) pre-test questions designed to emphasize the learning objectives; (2) description of the current gap in performance and need for increased education in the area of venous thromboembolism (VTE) prevention; and (3) a review of the epidemiology and prevalence of VTE in hospitalized medical patients, a review of the evidence behind current recommendations, and a review of the current American College of Chest Physicians (ACCP) recommendations for VTE prevention in hospitalized medical patients. Several months after release of the monograph, readers will be allowed to access an online link to case scenarios in which the application of their knowledge in VTE prevention will be tested. This will be ACCP-SEEK type questions, with case scenarios, followed by a multiple-choice question, and rationale of the correct and incorrect responses. CME credit will be provided.

TARGET AUDIENCE

Pulmonary and critical care medicine physicians

EDUCATIONAL OBJECTIVES

Following participation in this self-directed learning activity, the learner should be able to:

1. Understand the epidemiology and prevalence of venous thromboembolism (VTE) in hospitalized medical patients
2. Understand the options available (including their benefits and risks) for prevention of VTE in this population
3. Discuss the current American College of Chest Physicians (ACCP) recommendations for VTE prophylaxis in medical patients
4. Apply these recommendations to practice using case scenarios that will be provided in an online supplement to the publication

NEEDS ASSESSMENT

VTE including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the most common preventable cause of hospital death. The approximate annual incidence of VTE in the United States is 900,000 cases; it has been estimated that 300,000 Americans will die of PE each year. Hospitalization for an acute medical illness is associated with an eightfold increased risk of VTE. As such, prevention of VTE has become a national issue of quality care. Physicians may not be aware of or may not consistently use up-to-date evidence-based prevention guidelines. Since 1986, physicians have increasingly relied on the ACCP guidelines for recommendations on prevention. However, implementation of the recommendations has remained a challenge; there is an abundance of evidence documenting underutilization of prophylactic measures in hospitalized patients. Continuing medical education (CME) on VTE is important and can affect a change in physician behavior. Multimedia approaches and multiple interventions are more effective. As such, this educational activity will utilize both print and online media, with two separate interventions. It will be just one activity of many designed to address this core topic within the ACCP curriculum.

DISCLOSURES

The ACCP remains strongly committed to providing the best available evidence-based clinical information to participants of this educational activity and requires an open disclosure of any potential conflict of interest identified by our faculty members. It is not the intent of the ACCP to eliminate all situations of potential conflict of interest, but rather to enable those who are working with the ACCP to recognize situations that may be subject to question by others. All disclosed conflicts of interest are reviewed by the educational activity course director/chair, the Education Committee, or the Conflict of Interest Review Committee to ensure that such situations are properly evaluated and, if necessary, resolved. The ACCP educational standards pertaining to conflict of interest are intended to maintain the professional autonomy of the clinical experts inherent in promoting a balanced presentation of science. Through our review process, all ACCP CME activities are ensured of independent, objective, scientifically balanced presentations of information. Disclosure of any or no relationships will be made available on-site during all educational activities.

The following authors have disclosed to the ACCP that a relationship does exist with the respective company/organization as it relates to their presentation of material and should be communicated to the participants of this educational activity:

Andrew F. Shorr, MD, MPH, FCCP

Dr. Shorr has received funding as a consultant, speaker and advisor to GlaxoSmithKline and sanofi-aventis.

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ACCREDITATION STATEMENT

The American College of Chest Physicians is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

DESIGNATION STATEMENT

The American College of Chest Physicians designates this educational activity for a maximum of *2 AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Completion of this activity, including review of the pretest case questions, articles, post-test questions, and evaluation online, is estimated to take approximately 2 hours. This activity is available starting in February 2009. CME for this activity is available through February 28, 2010.

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Clinical Questions: Test Yourself

1. A 56-year-old man with a history of diabetes and hypertension is admitted to the hospital with new onset of congestive heart failure. His heart rate is 105 beats per minute, blood pressure is 138/88 mm Hg, respiratory rate is 22 breaths per minute, and he is afrebrile. His examination is notable for jugular venous distention, an S3 and S4 gallop, diffuse rales, and bilateral lower-extremity edema. Laboratory examination is notable for a blood urea nitrogen level of 57 mg/dL and a serum creatinine concentration of 2.2 mg/dL. Admitting orders for this patient should include:

A. Enoxaparin, 40 mg subcutaneously once daily

B. Enoxaparin, 20 mg subcutaneously once daily

C. Unfractionated heparin, 5,000 units subcutaneously twice daily

D. Fondaparinux, 2.5 mg subcutaneously once daily

2. Routine use of chemical prophylaxis in at-risk medical patients has been shown to:

A. Reduce the incidence of symptomatic pulmonary embolism

B. Reduce the incidence of fatal pulmonary embolism

C. Increase all-cause mortality

D. Increase the incidence of major bleeding

3. The use of low-molecular-weight heparin, as opposed to unfractionated heparin, for the prevention of venous thromboembolism in hospitalized medical patients:

A. Is associated with a greater pulmonary embolism risk reduction

B. Is associated with a greater deep vein thrombosis risk reduction

C. Is associated with decreased major bleeding

D. Is associated with decreased heparin-induced thrombocytopenia

Answers: 1. C, 2. A, 3. B

Prevention of VTE in Hospitalized Medical Patients: Just Do It!

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In its 2001 report, *Making Health Care Safer: A Critical Analysis of Patient Safety Practices,* the Agency for Healthcare Research and Quality (AHRQ) rated venous thromboembolism (VTE) prevention the number one patient safety intervention.[1] The reasons behind this highest rating took into account several factors, including the number of hospitalized patients at risk for VTE in the United States and around the world, the strong evidence of safe and effective VTE prevention options, and the overwhelming evidence of current underutilization of these options. The Institute of Medicine has defined the failure to provide adequate thromboprophylaxis to hospitalized, at-risk patients as a medical error.[2] Additionally, in September 2008, the Acting US Surgeon General, Rear Admiral Steven Galson, issued a Call to Action to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE).[2] DVT and PE are serious public health problems, and yet there is no national consensus on how to best approach these problems. The Surgeon General's Call to Action urges increased public awareness of VTE, the development of evidenced-based practices, and initiation of further research that can address gaps in current knowledge.

Hospitalized medical patients are at particularly high risk of developing a thrombotic event. Based on criteria established in the American College of Chest Physicians (ACCP) Guidelines, 51% to 53% of medical patients in US acute care hospitals are at risk for VTE.[3,4] In a multicenter chart audit of patients in 29 Canadian hospitals admitted for an acute medical illness, 90% had indications for thromboprophylaxis.[5] More recently, in a 32-country cross-sectional study, 42% of medical patients met "at risk" criteria.[6]

> *Hospitalized medical patients are at particularly high risk of developing a thrombotic event.*

However, guidelines that direct physicians in appropriate prophylactic interventions have existed for more than 20 years. In 1986, the "Third ACCP Consensus Conference for Antithrombotic Therapy" guidelines were published, which included 17 specific recommendations on VTE prevention.[7] Published in 2008, the 8th edition of the ACCP evidence-based clinical practice guidelines for antithrombotic and thrombolytic therapy included almost 100 evidence-based thromboprophylaxis recommendations in 9 different categories.[8]

Unfortunately, an abundance of evidence suggests that these guidelines are not routinely followed. The previously mentioned national, multicenter chart audit conducted in 29 Canadian hospitals over a 3-week period abstracted information concerning the indications and appropriateness of VTE prophylaxis according to the ACCP 2001 guidelines (6th edition). Fewer than 15% of these patients received the recommended preventive therapy.[5] In a multinational observational study involving hospitalized medical patients in 52 hospitals in 12 countries, 52% of US patients and 43% of patients in other countries met the ACCP criteria for VTE risk. Of these patients, only 61% received some form of VTE prophylaxis.[4] Additionally, an international cross-sectional survey involving 358 hospitals in 32 countries across 6 continents abstracted data about the risk for VTE according to the 2004 (7th edition) ACCP guidelines. Of the 42% of patients who met at-risk criteria, on average, only 50% received the recommended VTE prophylaxis, with a range of 0% to 83%.[6] Finally, a retrospective review of the HealthFacts database abstracted patients >40 years old who met ACCP (6th edition) criteria for VTE risk to determine if patients received recommended anticoagulants at the proper dosage for the proper duration.[9] Of the 123,304 hospital admissions that met inclusion criteria, 29,000 (23%) patients received some kind of VTE prophylaxis. Only 15% of the medical patients were receiving the recommended VTE prophylaxis. The most common error was omission of preventive measures.

The explanation for this gap in performance is likely multifactorial. Lack of awareness of the disease on the

part of both patients and the public is paramount. The existence of multiple guidelines, with overlapping and sometimes conflicting data, likely confuses many clinicians. The complexity of existing guidelines makes implementation difficult. Among different health care settings and specialties, there is disagreement about the true risk of thrombosis in many patient populations. Finally, many physicians are hesitant to use chemical prophylaxis because they overestimate the risk of bleeding complications related to these agents.

Changing physician behavior is not easy. The method that is most effective in increasing the adherence to established guidelines is not known. Deterrents to implementation vary by practice type and location, and the approach to gaps in performance likely needs to be individualized. Approaches shown to be effective in VTE prevention include electronic alerts,[10] clinical decision support systems,[11] and academic detailing.[12,13] In addition, benchmarking initiatives (such as the Surgical Care Improvement Process [SCIP],[14,15] which includes 2 VTE measures [prophylaxis ordered and prophylaxis given]) and regulatory programs (such as the National Quality Forum's Safe Practices and Consensus Standards for Prevention and Care of VTE) may direct a more standardized approach to this issue.[16,17]

The ACCP, as a leader in the development of evidence-based guidelines for the care of patients with VTE and whose members are leaders in the field, is poised to respond to the Surgeon General's Call to Action. This response includes increased education of specialists and primary care providers about the true risks of thrombosis, the risks of bleeding from proper administration of prophylactic anticoagulants, and the availability of and proper use of treatment options. All physicians and health care systems need to develop tools or algorithms for appropriate prophylaxis in medical patients. VTE and, especially, fatal PE are preventable in the majority of patients, and this treatment is safe and effective. It is time we "just do it!" ■

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Prevention of VTE in Medical Patients: Current Evidence and Recommendations

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Historically considered a complication of surgical or trauma care, approximately 50% to 70% of symptomatic venous thromboembolism (VTE) occurs in persons acutely hospitalized for medical conditions.[1] In a general medical population, many studies demonstrate that the incidence of deep vein thrombosis (DVT) ranges from 5% to 14%.[2-4] With more than 700,000 persons hospitalized annually for medical conditions,[5] the potential burden of VTE in nonsurgical settings is staggering. Clinicians and administrators must familiarize themselves with the most recent recommendations of the 8th American College of Chest Physicians (ACCP) consensus conference on antithrombotics.[6]

Cost of VTE

Given the astounding economic burden of VTE, clinicians should appreciate the actual costs related to VTE care. Estimates suggest that per patient costs for DVT and pulmonary embolism (PE) are more than $10,000 and $16,000, respectively. Interestingly, these costs are even higher for Medicare patients than for the general population, in whom the average costs for managing DVT and PE are $13,208 and $20,728, respectively. This difference reflects the longer length of stay seen in older patient cohorts. In the very old, the costs for DVT are approximately 25% higher. In those with a secondary diagnosis of VTE, which indicates likely acquisition during hospitalization, costs are lower but still significant: $7,594 for DVT and $13,018 for PE.[7]

Beyond just the costs related to length of stay, pharmacy costs related to VTE treatment may exceed $3,000 per case.

However, these figures are misleading in that they reflect only the short-term costs related to inpatient care. VTE is associated with multiple secondary and potentially hidden costs. For example, the potential for bleeding due to therapeutic anticoagulant therapy, recurrent VTE, and complications from the initial thromboembolic event (ie, persistent pulmonary hypertension, post-thrombotic syndrome, chronic venous stasis) are extensive. In fact, approximately 5.3% of patients experiencing a VTE are readmitted into the hospital within 1 year.[7] Costs for these readmissions are often higher than for the initial visit: $11,862 for DVT and $14,722 for PE.[7] Thus, from a societal as opposed to a hospital perspective, VTE results in a substantial drain on resources.

Beyond just the costs related to length of stay, pharmacy costs related to VTE treatment may exceed $3,000 per case. Outpatient pharmacy charges are also substantial. Clearly, given these direct and indirect costs, almost any strategy that systematically enforces VTE prevention in medical patients will be cost-effective if not cost-saving.

Risk Factors for VTE

Known medical risk factors for hospital-acquired VTE include underlying conditions such as age, comorbid illness (eg, congestive heart failure [CHF], malignancy, active infection), immobilization, and procedures performed (eg, placement of a central venous catheter). Given the prevalence of these risk factors in hospitalized patients, it is not surprising that DVT can be a common condition. More important, many trials of pharmacologic prevention suggest that most hospitalized patients have multiple risk factors for VTE and that these risk factors are additive. For example, in the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) study,[4] which enrolled more than 1,100 patients, significant risk factors found to increase the chance for inpatient development of VTE included age >75 years, presence of malignancy, prior history of VTE, and acute infectious processes.[8] On average, patients in MEDENOX had more than two risk factors, and the risk for DVT in the placebo arm approached 15%. Two other placebo-controlled trials of pharmacologic thromboprophylaxis

in medical patients—the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT)[3] and the Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)[2]—confirmed the significance and prevalence of these risk factors. However, not all medical patients face a similar risk for VTE, with some populations at exceedingly elevated risk. In stroke patients, up to 75% of patients with hemiplegia develop DVT and 20% develop PE[9,10] without prevention.

As medical knowledge and treatments continue to improve, life expectancy will improve, patients will live longer with multiple comorbid conditions (such as underlying malignancies, CHF, or stroke), more patients will survive an acute infectious disease and be bedridden, and more medical patients will develop VTE unless preventative measures are taken to address this growing problem in appropriately selected patients.

Recent Recommendations for Thromboprophylaxis

The ACCP guidelines suggest that thromboprophylaxis can be either chemical or mechanical (**Table**).[6] Mechanical DVT prophylaxis is recommended for medical patients at high risk for developing VTE, but who have a contraindication for chemical DVT prophylaxis (eg, active or recent bleeding, severe thrombocytopenia). Graduated compression stockings (GCSs) and intermittent pneumatic compression (IPC) devices reduce venous stasis and are effective in reducing risk of VTE in postoperative patients.[11] Unfortunately, adequate studies showing the efficacy of these devices in medical patients are lacking, and their use is, therefore, extrapolated from surgical data. This explains the weak grade for this recommendation. In one small study (n=80), graduated compression stockings improved venous volume and reduced the incidence of DVT following acute myocardial infarction.[12] Elastic stockings may also reduce the frequency of DVT in patients who have acute stroke based on a similarly small trial.[13] As a consequence, further investigation is required to determine a more definitive role for mechanical prophylaxis in the medical population.

Graduated compression stockings and intermittent pneumatic compression devices reduce venous stasis and are effective in reducing risk of VTE in postoperative patients.

Effective pharmacologic agents include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) such as dalteparin or enoxaparin, or a pentasaccharide such as fondaparinux. Evidence for the effectiveness of UFH is scant as there are few small studies comparing UFH with placebo. In the Thromboembolism Prevention in Cardiopulmonary Disease with Enoxaparin (THE-PRINCE) study,[14] in which 100 patients with pneumonia and CHF were randomized to receive 5,000 U of UFH three times daily versus placebo, the incidence of DVT was reduced from 26.0% to 4.0% with UFH. In another study consisting of 131 patients,[15] medical patients receiving 5,000 U of UFH twice daily had an incidence of DVT of only 1.6% compared to 10.4% in those who received placebo.

Evidence for LMWH and fondaparinux derives from larger, more robust clinical trials. In MEDENOX,[4] medical patients were assigned to receive one of two doses of a LMWH, enoxaparin (20 mg or 40 mg), or placebo. Primary outcome measures included development of VTE (defined as either DVT, PE, or both) between days 1 and 14, and secondary outcome measures included development of VTE between days 1 and 110. Of 1,102 patients enrolled, only 5.5% of the patients who received 40 mg of enoxaparin once daily developed VTE as compared to 14.7% of the patients in the placebo group and 15.0% of the patients who received 20 mg of enoxaparin ($P<0.001$). The lower incidence of DVT was maintained to 110 days with a 7.0% incidence in the enoxaparin 40-mg group versus 17.1% in the placebo group and 17.5% in the enoxaparin 20-mg group ($P<0.001$). There were no significant risks of bleeding or mortality between the three groups. There have been two major criticisms of this trial, which apply to other randomized controlled trials (RCTs) in this area. First, the study was placebo-controlled rather than comparator-controlled with UFH. Unfortunately, this was a requirement of regulatory agencies in order to obtain approval of enoxaparin for this indication. Second, patients underwent screening for DVT at day 14 if they had not suffered a clinically apparent clot. Much of the difference between enoxaparin and placebo arose because of the differences in rates of asymptomatic DVT. The clinical implications of asymptomatic DVT are

Table. Selected Recommendations on VTE Prevention From the ACCP Guidelines (8th Edition)[6]

Hospital Thromboprophylaxis Policy

1. For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed (Grade 1A).
2. We recommend that the local thromboprophylaxis strategy be in the form of a written, institution-wide thromboprophylaxis policy (Grade 1C).
3. We recommend the use of strategies shown to increase thromboprophylaxis adherence, including the use of computer decision support systems (Grade 1A), preprinted orders (Grade 1B), and periodic audit and feedback (Grade 1C). Passive methods such as distribution of educational materials or educational meetings are not recommended as sole strategies to increase adherence to thromboprophylaxis (Grade 1B).

Mechanical Methods of Thromboprophylaxis

1. We recommend that mechanical methods of thromboprophylaxis be used primarily in patients at high risk for bleeding (Grade 1A) or possibly as an adjunct to anticoagulant-based thromboprophylaxis (Grade 2A).
2. For patients receiving mechanical methods of thromboprophylaxis, we recommend that careful attention be directed toward ensuring the proper use of, and optimal adherence to, these methods (Grade 1A).

Medical Conditions

1. For acutely ill medical patients admitted to the hospital with CHF or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH (Grade 1A), low-dose UFH (Grade 1A), or fondaparinux (Grade 1A).
2. For medical patients with risk factors for VTE and for whom there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with GCSs or IPC devices (Grade 1A).

Acute Ischemic Stroke

1. For acute stroke patients with restricted mobility, we recommend prophylactic low-dose subcutaneous heparin or LMWH (Grade 1A).
2. For patients who have contraindications to anticoagulants, we recommend IPC devices or elastic stockings (Grade 1B).

Critical Care

1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A).
2. For critical care patients who are at moderate risk for VTE (eg, medically ill or postoperative general surgery patients), we recommend using LMWH or low-dose UFH thromboprophylaxis (Grade 1A).
3. For critical care patients who are at high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCSs and/or IPC devices at least until the bleeding risk decreases (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).

Source: Geerts et al[6]

unclear. However, these clots mandated therapy because allowing them to progress to assess their natural history would have been unethical, given that 10% to 20% of patients with DVT may progress to PE.

Likewise, PREVENT[3] was designed to determine the efficacy of another LMWH, dalteparin 5,000 IU given once daily, versus placebo for DVT prophylaxis in medical patients. The incidence of VTE served as the primary end point. Of 3,706 patients enrolled, the incidence of VTE was reduced from 4.96% in the placebo group to 2.77% in the treatment group (P=0.0015). The relative risk (RR) reduction was 0.55 (95% confidence interval [CI], 0.38–0.80). Bleeding risk and mortality did not significantly differ between the two groups.

The third randomized, double-blind, placebo-controlled trial assessed the safety and efficacy of fondaparinux, a synthetic pentasaccharide that is a selective inhibitor of activated factor Xa.[2] Investigators randomly assigned 849 patients to 2.5 mg of fondaparinux given once daily or placebo. Akin to MEDENOX and PREVENT, the primary efficacy outcome was incidence of VTE, which was 5.6% with fondaparinux compared to 10.5% with placebo; RR reduction was 47% (P=0.029). Bleeding risk was similar between the two groups (0.2 vs 0.2, respectively).

Theoretically, prevention and treatment of DVT should reduce the likelihood of developing PE, subsequent death, and other complications such as post-thrombotic syndrome and chronic venous stasis. The trials described above did not show a significant difference in morbidity and mortality between groups. These studies, though, were not designed to evaluate long-term sequelae of DVT and were underpowered to show reduction in other clinically important outcomes, such as PE.

Theoretically, prevention and treatment of DVT should reduce the likelihood of developing PE, subsequent death, and other complications such as post-thrombotic syndrome and chronic venous stasis.

To address this issue, a meta-analysis was performed to determine the pooled RRs for symptomatic PE, fatal PE, all-cause mortality, and major bleeding in medical patients who received anticoagulant prophylaxis compared to no prophylaxis.[16] In nine studies totaling 19,958 patients, symptomatic PE occurred in 0.20% of patients receiving pharmacologic prophylaxis compared to 0.49% who did not receive prophylaxis. The RR was statistically significant (0.43; 95% CI, 0.26–0.71), and the absolute risk reduction (ARR) was 0.29%. Of 19,510 patients, fatal PE occurred in 0.14% of the patients who received anticoagulant prophylaxis compared to 0.39% of the patients who received no prophylaxis. Additionally, these authors noted a statistically significant reduction in fatal PE (RR, 0.38; 95% CI, 0.21–0.69) with an ARR of 0.25%. For all-cause mortality, they found no difference. Interestingly, they noted no correlation between pharmacologic prophylaxis and major bleeding. Specifically, this occurred in 0.58% of the patients treated compared to 0.44% in the patients without prophylaxis. Thus, anticoagulant prophylaxis was not associated with a statistically significant increase in major bleeding (RR, 1.32; 95% CI, 0.73–2.37). According to this meta-analysis, the use of DVT prophylaxis significantly decreases the risk of PE without increasing bleeding risk or affecting overall mortality. For approximately every 400 patients given pharmacologic prophylaxis, one PE can be prevented.

Comparison of Agents

How should clinicians choose among agents? The guidelines suggest multiple options exist and few trials have compared one pharmacologic agent to another. Hence, the choice must be individualized. However, newer data are emerging on this issue. A recent meta-analysis explored trials comparing heparin to placebo and outcomes in trials studying LMWH versus UFH.[17] Both UFH and LMWH were associated with major reductions in rates of DVT compared to placebo. Additionally, a three-times-daily regimen of UFH was more efficacious than a twice-daily approach. This conclusion, though, was based on an extrapolation of analyses comparing either regimen to placebo. There are no true RCTs comparing twice-daily to three-times-daily UFH. There are, alternatively, nine studies that cumulatively include more than 5,000 patients who received LMWH versus UFH for DVT prevention in medical patients. LMWHs led to a more than 30% RR reduction for DVT. The ARR was less impressive (1.7%) but suggests that for every 60 subjects given LMWH rather

than UFH, one additional DVT will be prevented. In the meta-analysis, although LMWH was associated with a 40% reduction in PE risk, this difference was not statistically significant (P=0.20). The authors observed no difference in either major bleeding or death as a function of whether UFH or LMWH was employed. An earlier meta-analysis suggested that LMWHs may be associated with less major bleeding, but that analysis included fewer studies and did not consider that major bleeding was defined differently across the various clinical trials reviewed.[18]

At present, there are no RCTs comparing fondaparinux to either UFH or LMWH for VTE prevention in medical patients. Hence, because of the various different pharmacologic profiles of these molecules and differences in patient characteristics, along with the acquisition costs of these agents, institutions need to review the data carefully to determine which options likely will work best. Adoption of protocols could shift the burden away from the clinician trying to remember to choose an agent for VTE prevention to a system where VTE prophylaxis will be given unless otherwise decided (eg, changing the default scenario). One large recent RCT[19] showed that mandating prevention and shifting the burden of proof toward giving prophylaxis rather than having to proactively order it was associated with enhanced rates of prophylaxis and reduced the rate of clinically significant VTE at 90 days.

VTE prophylaxis in ischemic stroke cerebrovascular accidents (CVAs) remains an increasing burden in US hospitals, and stroke patients face an exceedingly high risk for VTE. Specifically, the prevalence of VTE in patients who have experienced an ischemic stroke (ie, CVA) may approach 70%, whereas 1% to 2% with hemiplegia after CVA have a fatal PE.[10,20] In a meta-analysis that included three studies totaling 2,028 patients, VTE occurrence was significantly reduced with the use of LMWH compared to UFH (odds ratio [OR], 0.54; 95% CI, 0.41–0.70; P<0.001).[21] Intracranial hemorrhage was rare, occurring with a frequency of 0% to 0.8% in the three studies. There was no difference based on heparin type in the risk for intracranial hemorrhage (OR with LMWH, 0.75; 95% CI, 0.21–1.91; P=0.567) or major bleeding (OR with LMWH, 1.75; 95% CI, 0.73–4.20; P=0.551). Overall mortality also did not significantly differ between the LMWH and UFH groups (OR with LMWH, 0.97; 95% CI, 0.69–1.33; P=0.633).

Few studies have been done comparing LMWH to UFH for DVT prevention after CVA. In this meta-analysis, LMWH was superior to UFH in preventing asymptomatic VTE without increased risk of intracranial or overall bleeding. Use of either agent did not affect overall mortality following ischemic strokes.

VTE Prophylaxis in Critically Ill Patients

Critically ill patients are at increased risk for VTE not only because of their underlying conditions, but also because of the procedures and processes used to deliver critical care. As many as 10% of patients in the intensive care unit (ICU) receiving UFH prophylaxis develop a DVT, whereas 90% are clinically silent.[22] Unfortunately, few RCTs have been conducted in critically ill patients. One study randomized critically ill medical patients to receive 5,000 U of UFH twice daily versus placebo.[15] The incidence of VTE decreased from 29% to 13% with the use of thromboprophylaxis (P<0.05). In the second study,[23] mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) were randomized to receive a LMWH, nadroparin, or placebo. VTE rates fell from 28.2% to 15.5% with thromboprophylaxis (P=0.045).

Current recommendations for DVT prevention in the critically ill medical patient include the use of either UFH or LMWH. The Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT) is a multicenter, randomized clinical study that is being currently conducted in an attempt to determine safety and efficacy of these agents. Hopefully, the results of this study will clarify the role of these agents as thromboprophylactic agents in critically ill patients. There are no clinical trials of mechanical devices for VTE prevention in ICU patients.

Conclusion

Acutely ill medical patients clearly face an increased risk for VTE. Use of DVT prophylaxis can significantly reduce the incidence of DVT, its potential sequelae, and costs associated with treatment of VTE. Thus, the ACCP (8th edition) guidelines recommend the use of thromboprophylaxis with LMWH, UFH, or fondaparinux in those patients with risk factors for developing VTE.[6] If there is a contraindication to anticoagulant prophylaxis, mechanical prophylaxis with GCSs or IPC devices should be used. ■

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