Venous thromboembolism (VTE) is an important medical problem that affects millions of patients each year. With appropriate prophylaxis, many of these thromboembolic events can be prevented. Although strong evidence supporting VTE prophylaxis spans several decades, several large American and global registries have documented very poor use of appropriate prophylaxis. Because of increasing regulatory requirements, hospitals nationwide are in the process of developing documentation of appropriate VTE prophylaxis programs for both surgical and medical patients. A wide range of clinicians must understand what constitutes appropriate VTE prophylaxis in various patient populations. With the existence of numerous pharmacologic agents, abundance of data from major clinical trials, and several nationally recognized clinical guidelines, compiling the needed reference material to make evidence-based decisions on appropriate VTE prophylaxis can be difficult for clinicians. Therefore, we provide a bibliography of key articles and guidelines related to the prevention of VTE in various patient groups. We hope this compilation will serve as a resource for pharmacists, physicians, nurses, residents, and students responsible for the care of patients who may be at risk for VTE.

Key Words: anticoagulation, evidence-based medicine, pharmacy practice.

preventable mortality and excessive hospital charges. Clinicians must realize that many thromboembolic events can be prevented with appropriate VTE prophylaxis. Despite more than 30 years of demonstrated effectiveness and safety, VTE prophylaxis is substantially underutilized. This underutilization has led to the recent involvement of government and other regulatory agencies in an attempt to improve VTE prophylaxis in U.S. hospitals.

The Cardiology Practice and Research Network (PRN) of the American College of Clinical Pharmacy has taken the initiative to compile lists of key articles and guidelines in major focus areas of cardiology. From 2004-2006, five collections of annotative bibliographies were published on the topics of acute coronary syndromes, arrhythmias, hypertension, systolic heart failure, and dyslipidemias. These documents are being updated and published in Pharmacotherapy. Since the prevention of VTE is not only a cardiology issue, the Cardiology PRN joined with the Internal Medicine PRN and the Ambulatory Care PRN to compile this document that focuses on key articles and guidelines in the prevention of VTE. We collected guidelines and significant articles published in the area of VTE prevention and provide a summary of the results of the clinical trials, as well as clinical insights on the implications for clinical practice and research. This document will serve as an excellent review and resource for pharmacists, physicians, nurses, residents, and students, especially in this time of increased attention on VTE prevention.

Clinical Guidelines


The 8th edition of the American College of Chest Physician (ACCP) guidelines, published in the summer of 2008, provides updated recommendations on the prevention of VTE in a wide variety of patient populations. In relation to other clinical practice guidelines on VTE prevention, the ACCP guidelines are the most comprehensive in terms of patient populations discussed, and often are the primary guideline source that most clinicians turn to regarding not only recommendations for the prevention of VTE, but also the appropriate use of antithrombotic agents in general. General recommendations include that every hospital should develop and implement a formal, institution-wide strategy to assess each patient for risk of VTE. The guidelines also encourage specific resources such as computer decision support, preprinted orders, and periodic audit to facilitate appropriate use of VTE prophylaxis. In a change from the 7th edition published in 2004, the 8th edition outlines a risk assessment scheme with three levels of risk, as opposed to four levels in the previous version. Low-risk patients include those undergoing minor surgery or patients who are fully mobile with medical conditions. Patients at moderate risk include most patients undergoing general surgery, open gynecologic surgery, or urologic surgery, as well as patients who are confined to bed rest with medical conditions. High-risk patients include those undergoing major orthopedic surgery and those with major trauma or spinal cord injury (SCI). General recommendations for the prevention of VTE depending on risk level are as follows: low risk—early ambulation, no specific preventive interventions needed; moderate risk—low-molecular-weight heparin (LMWH) at recommended doses, low-dose unfractionated heparin...
(UFH) given 2 or 3 times/day, fondaparinux, or mechanical methods in patients at high risk for bleeding; high risk—LMWH at recommended doses, fondaparinux, and warfarin with dosage titration to an international normalized ratio (INR) of 2.0–3.0. Low-dose UFH tends to be less effective than other pharmacologic options and should be used in conjunction with mechanical methods in high-risk patients. Given the comprehensive nature of the guidelines, the reader is referred to the parent document for more details regarding recommendations in specific patient populations.

Other recommendations should be noted. First, aspirin alone should never be recommended for prophylaxis in any patient group. Second, careful attention to renal function should be a factor in the selection of the specific agent for prophylaxis. When considering the use of agents that accumulate in the urine, health care practitioners should avoid the use of these agents, use a reduced dosage of the agent, or monitor the drug level or anticoagulant effect of the agent if applicable. Finally, when mechanical methods of prophylaxis are selected, careful attention should be paid to ensuring that they are used properly.


Noting that the risk of developing VTE events can be significant in patients undergoing major gynecologic surgery (estimated rates of 15–40% in the absence of prophylaxis), the American College of Obstetricians and Gynecologists developed guideline to address recommendations for prevention of DVT and pulmonary embolism. In terms of defining the risk of VTE in gynecologic surgery, the authors make use of the four-level risk scheme that was found in the 7th edition of the ACCP guidelines published in 2004. Additional sections of the guideline discuss the available mechanical and pharmacologic options for prophylaxis, as well as the role of hypercoagulable states in the development of VTE. Recommendations for VTE prophylaxis in gynecologic surgery based on risk are as follows: low risk—no specific prophylaxis intervention is recommended other than early ambulation; moderate risk—low-dose UFH 5000 U subcutaneously twice/day, dalteparin 2500 IU subcutaneously once/day, enoxaparin 40 mg subcutaneously once/day, graduated compression stockings (GCS), or intermittent pneumatic compression (IPC) devices are all equivalent options; high risk—low-dose UFH 5000 U subcutaneously 3 times/day, dalteparin 5000 IU subcutaneously once/day, enoxaparin 40 mg subcutaneously once/day, or IPC devices are all equivalent options; highest risk—low-dose UFH 5000 U subcutaneously 3 times/day, dalteparin 5000 IU subcutaneously once/day, enoxaparin 40 mg subcutaneously once/day, GCS, or IPC device plus recommended doses of low-dose UFH or LMWH are all equivalent options. Recommendations are based on available literature in the gynecologic surgery arena for prevention of VTE.

Other recommendations should be noted. First, clinicians must appropriately consider the timing of dose administration and placement or removal of epidural anesthesia to minimize the risk of spinal hematoma. Second, if mechanical methods are to be used, they should be started at the beginning of surgery. Third, the authors do not recommend the discontinuation of hormone replacement therapy or contraceptives before gynecologic surgery because of the lack of evidence that discontinuation of these agents reduces the risk of postoperative VTE. Finally, it is reasonable for patients with a history of VTE to undergo testing for hypercoagulable conditions.


Recognizing that there exists a close relationship between cancer and the occurrence of VTE, and that there are some distinct aspects in prevention or treatment of VTE in patients being treated for malignancy, the American Society of Clinical Oncology developed this guideline, which encompasses recommendations for both prevention and treatment of VTE in patients with cancer. In addition, as a rationale for developing this document, the authors cite the relative lack of focus on patients with cancer in the 2004 version of the ACCP guidelines. Although patients with cancer share many of the same risk factors for VTE as the general population, specific risk factors in patients with malignancy include the following: time since cancer diagnosis, with the highest risk in the first 3–6 months; current metastatic disease; primary site of malignancy; active chemotherapy; and current...
or recent antiangiogenic therapy with thalidomide, lenalidomide, or bevacizumab.

The guideline was developed to address five primary questions on the prevention or treatment of VTE in patients with cancer. Only the questions related to prevention of VTE will be addressed here. First, hospitalized patients with cancer should be considered candidates to receive prophylaxis with low-dose UFH, LMWH, or fondaparinux in the absence of contraindications; this recommendation is based on trials of medically ill patients that contained subsets of patients with cancer. Second, routine prophylaxis for ambulatory patients without VTE and receiving chemotherapy is not indicated. The only exception is patients with myeloma who are receiving thalidomide or lenalidomide plus chemotherapy or dexamethasone. In those cases, an LMWH or warfarin (INR target 1.5) should be used for prevention of VTE. Finally, all patients undergoing major surgical interventions for malignant disease should receive prophylaxis with low-dose UFH, LMWH, or fondaparinux in the absence of contraindications. Prophylaxis should extend for at least 7–10 days. Mechanical methods of prophylaxis such as IPC may be added to pharmacologic agents but should not be used alone unless that patient is at high-risk for bleeding. In addition, it is reasonable to use LMWH for prophylaxis for up to 4 weeks after surgery in patients thought to be at very high risk, defined as major abdominal or pelvic surgery with residual malignant disease, obesity, or previous history of VTE.


Despite being more than 5 years old, these recommendations remain the primary source for how to handle anticoagulation in patients also receiving neuraxial anesthesia and analgesia in the perioperative period. This issue first came to the forefront in the 1990s with the release of a number of case reports in which patients had developed spinal hematomas associated with the use of neuraxial anesthesia. Although LMWHs were used in many of these cases, it is important to note that many patients had hemostatic abnormalities and had received other agents that may affect hemostasis (aspirin, nonsteroidal antiinflammatory drugs, UFH). Common themes of all the recommendations include consideration for the timing of needle placement, epidural catheter removal, and drug administration. In patients receiving recent fibrinolytic therapy, the use of spinal or epidural anesthesia should generally be avoided. In addition, general guidelines for fibrinolytics suggest avoiding their use in patients with puncture of noncompressible vessels in the past 10 days. In patients receiving low-dose UFH subcutaneously, there is no contraindication to neuraxial techniques, as the risk for developing spinal hematoma appears to be minimal. In patients who are to receive intraoperative anticoagulation with UFH, the UFH infusion should be started at least 1 hour after needle placement, and indwelling catheters should be removed 2–4 hours after discontinuation of the UFH infusion and only after the patient's coagulation status has been assessed.

In patients for whom LMWH is being used for VTE prophylaxis, concomitant use of other oral antiplatelet and anticoagulant drugs should be avoided. Also, needle placement should be delayed until 10–12 hours after the dose of LMWH, when LMWH is being started preoperatively. If LMWH has been administered in treatment doses, needle placement should commence at least 24 hours after the last dose. Finally, postoperative LMWH prophylaxis should begin no sooner than 2 hours after needle or indwelling catheter removal. In patients who had been receiving long-term warfarin therapy or are receiving warfarin therapy for VTE prophylaxis, long-term warfarin therapy ideally should be held for a minimum of 4–5 days before surgery, and assessment of the INR should be undertaken before needle insertion. In patients receiving preoperative warfarin for prophylaxis, an INR should be checked before needle placement if it has been over 24 hours since the first dose, or if two or more doses of warfarin have been given. For patients with an indwelling catheter who are receiving warfarin, the catheter should be removed when the INR is less than 1.5. The use of fondaparinux and neuraxial anesthesia or analgesia should follow the conditions used in clinical trials as closely as possible. Additional recommendations are provided regarding the use of antiplatelet agents and herbal therapy. In either case, significant risk for spinal hematoma is noted only with the use of adenosine diphosphate antagonists, such as ticlopidine and clopidogrel, and glycoprotein IIb-IIIa antagonists.

The guidelines from the American Academy of Orthopedic Surgeons (AAOS) have generated a high level of controversy and debate. Although the guidelines have not been peer reviewed, nor have they been published in a peer-reviewed journal, the AAOS thoroughly documents the systematic process used to produce their conclusions. Therefore, readers can make their own interpretations and conclusions regarding the methods used as if the document were a published article. Important differences guide the development of AAOS recommendations as compared with other guidelines that address VTE prevention. First, the authors of the AAOS guidelines question the relationship between the prevention of DVT and a subsequent decrease in pulmonary embolism. Whereas most consensus guidelines and systemic reviews take the approach that interventions that have supporting evidence for lowering the risk of DVT will also lower the risk of pulmonary embolism, the authors of AAOS guidelines state that there is little compelling literature validating this relationship. Second, as such, the authors of the AAOS guidelines by default place little emphasis on the complications of DVT development such as venous insufficiency, postthrombotic syndrome, and recurrent events. Finally, although bleeding is discussed and emphasized in other clinical guidelines on VTE prevention, the AAOS authors place a higher degree of emphasis on the risk of bleeding in the development of their recommendations, citing that bleeding may result in chronic joint stiffness, infection, and potentially a return to surgery for evacuation of hematomas. The authors also speculate that the reported rate of bleeding in clinical trials is an underestimate of real-world experience. Consequently, the recommendations for VTE prevention in this clinical guideline focus solely on an intervention’s capacity to reduce the frequency of clinical pulmonary embolism, as well as to cause major bleeding.

The availability of extensive literature on the prevention of DVT by various pharmacologic modalities is given minimal consideration. The consensus document provides recommendations for the preoperative, intraoperative, and postoperative periods. The recommendations for prevention of symptomatic pulmonary embolism in patients at standard risk for both pulmonary embolism and major bleeding include aspirin 325 mg/day for up to 6 weeks, LMWH dosed according to the package insert for 7–12 days, fondaparinux dosed according to the package insert for 7–12 days, and warfarin with goal INR less than 2.0 for 2–6 weeks. In patients with an elevated risk for pulmonary embolism but standard risk for major bleeding, only LMWH, fondaparinux, or warfarin is recommended. In patients at high risk for bleeding, regardless of the risk of pulmonary embolism, only aspirin and warfarin are recommended as options. It is important to note that while aspirin has been shown to be effective at preventing DVT compared with placebo, it has consistently been shown to be inferior to anticoagulant options at preventing DVT. Hence, the recommendation for the use of aspirin for prophylaxis is not found in other clinical guidelines and often is actively discouraged. Resolving the discrepancy over recommendations for aspirin use for prophylaxis in various clinical guidelines continues to be one of the challenges in improving the rates of VTE prophylaxis for patients requiring acute care.


The goal of this consensus document was to provide clinical guidance to physicians regarding the appropriate use of vena cava filters, especially those that may be removed after a period of time. In 2003, the United States Food and Drug Administration approved changes to instructions for several available vena cava filters such that they could be used on a temporary basis. Subsequently, the overall use of vena cava filters increased, especially with nonpermanent devices. Although physicians now had technical instructions on how to place and remove nonpermanent filters, no information was available regarding which patients could be candidates for a removable filter or what specific considerations to evaluate before placing a removable filter. To further complicate matters, available literature addressing the use of vena cava filters, either permanent or removable, is sparse at best, with most reports being in the form of observational studies.

In 2005, the Society of International Radiology
convened a multidisciplinary consensus conference to develop guidance for the use of nonpermanent filters. The consensus group advocates several general principles. The primary means of prophylaxis and treatment of VTE are pharmacologic in nature. The sole indication for use of a vena cava filter is the prevention of pulmonary embolism in patients who cannot receive pharmacologic prophylaxis or treatment, or who despite pharmacologic prophylaxis or treatment remain at unacceptably high risk for pulmonary embolism. The indications for use of a nonpermanent vena cava filter are no different from those for the use of permanent filters. The decision to use a nonpermanent filter should be based on the anticipated required duration of protection from pulmonary embolism, as well as the time period in which pharmacologic therapy may be contraindicated—when either or both of these are transient, the use of a retrievable filter can be justified. Regardless of whether a filter is in place, pharmacologic prophylaxis or treatment should be started as soon as it is determined safe to do so. And finally, whereas the placement of vena cava filters to prevent pulmonary embolism in patients who have no objectively confirmed acute DVT events is controversial and has little support in the literature, there are patient populations in which some support is available and use seems reasonable. These include those who sustained major trauma, critically ill patients with a history of VTE and contraindications to anticoagulation, and those undergoing bariatric surgery. The guideline contains additional information regarding the removal of nonpermanent vena cava filters. Important management points include the absence of a need to discontinue therapeutic anticoagulation during the removal of a temporary filter, and, after filter retrieval, patients should be treated according to their VTE status according to standards of care as delineated in national guidelines.

Clinical Predictors, Incidence, Prevalence, and Risk Stratification


This landmark study is the first in a series conducted by this research group examining the incidence of and risk factors for VTE. The purpose of this initial investigation was to characterize trends in the incidence of DVT and pulmonary embolism over a prolonged period of time, specifically 1966–1990. The researchers used a retrospective, population-based study design whereby they identified all known cases (2218 cases) of first-lifetime DVT or pulmonary embolism from medical records, death certificates, and autopsy reports from residents of Olmsted County, Minnesota. In all cases included in the analysis, the diagnosis of DVT or pulmonary embolism was determined by objective methods. The mean age of patients in these first-time VTE cases was approximately 62 years. Forty-two percent had DVT, 44% had pulmonary embolism, and 14% had both DVT and pulmonary embolism at the time of diagnosis. The average annual incidence of VTE over the 25-year period was 117/100,000 patients. The average annual incidence of pulmonary embolism with or without DVT (69/100,000 patients) was somewhat higher than the annual incidence of DVT alone (48/100,000 patients). Among adults younger than 45 years, women were more likely to experience a VTE than men, but the reverse was true after the age of 45 years. The overall lifetime incidence of VTE was slightly greater in men (male:female ratio 1.2:1). As expected, the incidence of VTE increased markedly with age—nearly doubling with each decade after the age of 40 years. The annual incidence of VTE over time was not constant. There was a notable 35% decline in the average annual incidence of pulmonary embolism between 1977 and 1979, which may have been due to changes in diagnostic testing patterns, improvements in the care of patients with DVT, and/or a decline in the rate of autopsy. Regardless of the explanation for this unexpected observation, this study clearly demonstrated that VTE is a common disease and its occurrence among the elderly is quite high. Perhaps the most surprising finding of this study was the relatively high incidence of pulmonary embolism (with or without DVT). Indeed, many cases of pulmonary embolism were identified by autopsy alone—suggesting that many patients do not present with classic VTE symptoms and/or they die suddenly. In either case, pulmonary embolism is far more common than previously realized, and as the population ages and high-risk surgeries are performed more frequently, the problem is likely to escalate.

Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease

The association between cancer and thrombosis is well established and was first characterized by Trousseau in 1865. Patients with an active malignancy are significantly more likely to develop VTE, and likewise, patients with an idiopathic or unprovoked VTE are far more likely to receive a diagnosis of malignancy. Given that cancer is a heterogeneous group of diseases, this study attempted to quantify the incidence of DVT and pulmonary embolism associated with specific types of malignancy. Further, the researchers wished to determine if the rate of recurrent VTE was greater in patients with malignancy than in patients who have VTE unrelated to malignancy. The investigators constructed a retrospective analysis by using Medicare Provider Analysis and Review Record (MEDPAR) data from 1988–1990. The MEDPAR database includes data regarding nearly every hospital admission, including primary and secondary diagnosis codes, for Medicare recipients. The incidence of initial VTE and recurrence over 183 days after the initial event was determined in four mutually exclusive groups based on initial hospitalization discharge diagnosis: patients with both DVT or pulmonary embolism and a malignant disease; patients with DVT or pulmonary embolism without malignant disease; patients with malignant disease without DVT or pulmonary embolism; and patients with nonmalignant disease without DVT or pulmonary embolism. Although the cumulative probability of hospitalization for VTE in patients with malignancy (0.6%) over the 3 years was only slightly greater than that in patients without malignancy (0.57%, p=0.001), the rates of VTE among different types of cancers were strikingly different. The rates of VTE among patients with ovarian (120/10,000 patients), brain (117/10,000 patients), and pancreatic (110/10,000 patients) cancers were 5–8 times greater than the rates observed in those with head and neck (16/10,000 patients), bladder (22/10,000 patients), and breast (22/10,000 patients) cancers. Other common malignancies such as prostate, colon, and lung cancers had rates of VTE of 61–79/10,000 patients. The investigators also found that the cumulative probability of re-admission with a VTE over the next 183 days was significantly greater in patients with malignancy and VTE (22%) when compared to patients with VTE without malignancy (6.5%), those with malignancy without VTE (13.5%), or those with nonmalignant disease without VTE (8%). Likewise, the probability of death was significantly higher in those patients with a discharge diagnosis of malignancy and VTE (94%) compared to those with malignancy alone (42%), no malignancy (29%), and VTE without malignancy (26%).

Whereas the generalizability of these data is somewhat limited due to the older age of the population sample, the findings clearly show that the risk of VTE is significantly different among the various types of malignancy and that the risk of recurrent VTE and death is very high among those patients with the two diagnoses. Indeed, in the absence of autopsy data, it seems likely that a substantial proportion of the deaths in the VTE with malignancy group were attributable to fatal pulmonary embolism or to bleeding complications related to anticoagulation therapy.


The primary objectives of this case-control study were to identify independent risk factors for VTE and to estimate the magnitude of risk imparted by each. Using data from the Rochester Epidemiology Project, the researchers identified all known patients from Olmsted County, Minnesota, with a first-lifetime VTE event between 1976 and 2000 (625 patients), and compared them with 625 age-, sex-, and calendar-year–matched controls. The diagnosis of VTE among case patients was confirmed by objective means. Over 500 different clinical parameters were collected from the medical records of the case patients and control subjects by trained abstractors. Step-wise conditional logistic regression analysis was performed on the data to create a final model, and a bootstrap method was used to validate the variables selected. The factors most powerfully associated with a first-time VTE were surgery (odds ratio [OR] 21.7), trauma (OR 12.7), and recent hospitalization or nursing home confinement (OR 8.0). Other factors that conferred considerable risk were malignancy with (OR 6.5) or without (OR 4.5) chemotherapy, central venous catheter (CVC) or pacemaker placement (OR 5.6), and neurologic disease with extremity paresis (OR 3.0). A history of superficial vein thrombosis (OR 4.3) also appeared to increase the likelihood of VTE, as did varicose veins before the age of 45 years (OR 4.2) but not later
among female patients, the postpartum period (OR 19) and gynecologic surgery (OR 11) were also found to increase the risk of VTE. Not surprisingly, serious liver disease (OR 0.1) protected against VTE.

This study confirmed that surgery, trauma, and hospitalization were all strong and independent risk factors for the development of VTE. However, given the relatively small number of cases in this cohort study, the risk associated with less frequently encountered factors such as inflammatory bowel disease, chronic kidney disease, and oral contraceptive use could not be accurately estimated. Moreover, information regarding inherited thrombophilias was not available. Finally, the study population was restricted to residents of Olmsted County, Minnesota, which limits the generalizability of the findings.


The authors of this review article regarding inherited prothrombotic states give readers a qualitative overview of the subject and propose a simplified classification scheme. The authors segment the major hereditary thrombophilias into two major groups: group 1 being disorders caused by a deficiency of coagulation factor inhibitors, and group 2 being disorders caused by increased levels or function of coagulation factors. Group 1 disorders include deficiencies of antithrombin, protein C, or protein S. Group 2 disorders include activated protein C resistance (or factor V Leiden); factor II (prothrombin) G20210A mutation; elevated levels of factors VIII, IX, and XI; evaluated levels of lipoprotein(a); and dysfibrinogenemia. Disorders in group 1 are relatively uncommon, with a prevalence in the general population estimated to be less than 0.5%. However, among patients with an unprovoked or idiopathic VTE, as many as 7.5% have a group 1 deficiency. Group 1 deficiencies generally impart a greater lifetime risk of VTE when compared with group 2 disorders. Some of the group 2 disorders are relatively common in the general population. Upward of 5–6% of healthy Northern Europeans have factor V Leiden. Similarly, the prothrombin gene mutation has been found in 4% of the general population in some parts of the world. Although group 2 disorders clearly increase the lifetime risk of VTE, it is uncommon for them to be the primary cause. In other words, group 2 disorders are a contributing factor that increases the likelihood of VTE in patients with other underlying risks such as surgery, trauma, estrogen use, or acute medical illness requiring hospitalization. Given the prevalence of group 2 disorders in the population, co-inheritance of two prothrombotic states is not uncommon, and the risk imparted by each disorder appears to be additive. Whether clinicians should routinely obtain a “hypercoagulable work-up” in patients who have an idiopathic or seemingly unprovoked VTE at presentation is controversial. It remains unclear whether this information would alter the intensity or duration of antithrombotic treatment. Nevertheless, a working knowledge of the most common thrombophilias, their relative prevalence, and the relative risk (RR) for VTE that each imparts will help clinicians interpret the literature and understand the context of future clinical trials.


Written by two of the most frequently cited VTE epidemiology researchers, this comprehensive review examines the evidence implicating a breadth of risk factors associated with VTE. The authors stratified these risk factors into two broad categories: individual risk factors that are sufficient to justify the use of antithrombotic drugs for prophylaxis, and factors that increase VTE risk but are not sufficient individually to justify pharmacologic approaches for prevention. The strongest risk factors for VTE (OR > 10) include hip or leg fracture, hip or knee replacement, major general surgery, major trauma, and SCI. The use of antithrombotic drugs is clearly warranted in these populations. Factors that place patients at moderate risk (OR 2–9) include previous VTE, arthroscopic knee surgery, malignancy, CVCs, cancer chemotherapy, heart failure, respiratory failure, pregnancy or postpartum period, oral contraceptives, hormone replacement therapy, and thrombophilia. Among these moderate risk factors, the authors suggested that malignancy, heart failure, and respiratory failure pose sufficient risk to warrant pharmacologic prophylaxis during hospitalization—a premise that has been confirmed by randomized clinical trials. It is important to note that thrombophilias, such as antithrombin deficiency, protein C or S deficiency, activated
protein C resistance or factor V Leiden, and the factor II G20210A mutation, are not, in and of themselves, considered sufficiently strong risk factors to warrant primary prophylaxis with antithrombotic drugs. Factors that are relatively weak contributors to VTE risk (OR < 2) included bed rest for more than 3 days, prolonged sitting (e.g., due to car or air travel), increasing age, obesity, and varicose veins. These risk factors are additive, and most patients who develop VTE will have two or more identifiable risk factors.


This research report is an extension of the authors’ data regarding VTE risks previously reported in the Archives of Internal Medicine in 2000. The purpose of this study was to specifically examine the risk for VTE during pregnancy and the postpartum period, as well as trends over time. Using data from the Rochester Epidemiology Project, the researchers identified 100 women known to have had a DVT or pulmonary embolism during pregnancy or the postpartum period (e.g., up to 3 mo after the termination of pregnancy) in Olmsted County, Minnesota, between 1966 and 1995. The absolute risk of VTE during pregnancy and postpartum period combined was approximately 200/100,000 woman-years. This represents an RR for VTE of 4.2 among pregnant and postpartum women compared with the expected age-specific rate of VTE among women living in Olmstead County. The annual incidence of VTE was significantly greater among postpartum women (511/100,000 patient-yrs) when compared with pregnant women (96/100,000 patient-yrs). Moreover, the annual incidence of pulmonary embolism was substantially greater in postpartum women (160/100,000 patient-yrs) when compared with pregnant women (11/100,000 patient-yrs). Younger women (aged 15–19 yrs) were more likely to experience a DVT during pregnancy than older women, but the incidence of VTE, particularly pulmonary embolism, increased with age during the postpartum period. Trend analysis over 30 years revealed that the incidence of VTE during pregnancy remained essentially unchanged, but the incidence of pulmonary embolism during the postpartum period decreased by greater than 2-fold with a notable decrease observed from 1985–1995. The authors postulate that this finding may be due to shorter hospital stays and earlier mobilization of women after delivery. Although the generalizability of this study is limited because of the narrow population studied (98% Caucasian), the findings are a reminder that the postpartum period places women at greater risk for VTE. Whether universally screening women during the first trimester of pregnancy and using appropriate interventional strategies (e.g., GCS) for those at most risk would lower the frequency of VTE during pregnancy is unknown.


This concise review by a longstanding and passionate proponent for universal risk assessment is an excellent guide for clinicians and clinical administrators; it uses concrete examples to improve the quality of patient care. Included in the article is Evanston Northwestern Healthcare’s Thrombosis Risk Factor Assessment score sheet that the author and his colleagues developed in the late 1980s. They have used and refined this instrument over many years based on “science, logic, emotion, and experience.” The Thrombosis Risk Factor Assessment instrument is a practical tool that can be completed by any health care practitioner based on easily obtained information gathered during a patient interview supplemented by the medical record. The tool helps practitioners weigh the relative strength of each risk factor by scoring them from 1–5 points. Risk factors awarded only 1 point are considered relatively minor contributing causes, whereas those risk factors awarded higher points are of relatively greater strength and importance in terms of VTE risk. The cumulative total risk factor score is determined by simple addition. Patients with a Thrombosis Risk Factor Assessment score of greater than 2 should receive VTE prophylaxis, using either a mechanical or pharmacologic method. Patients with a Thrombosis Risk Factor Assessment score of 5 or more should receive pharmacologic prophylaxis alone or in combination with a mechanical method. The tool also provides the clinician guidance regarding potential safety issues that must be considered before beginning pharmacologic strategies. For practitioners and institutions that are struggling to create a VTE risk assessment instrument, the simple but effective tool described in this review is extremely helpful.
As the title implies, the objective of this study was to determine the total number of patients admitted to U.S. hospitals in 2003 who were at risk for VTE. The investigators used the 2003 Nationwide Inpatient Sample from the Healthcare Cost and Utilizations Project to determine the total number of patients at risk. The Nationwide Inpatient Sample is a robust all-payer inpatient database with information regarding approximately 8 million hospital stays from nearly 90% of hospitals in the United States. Adults (age > 18 yrs) who were admitted to the hospital for at least 2 days were considered potentially eligible for VTE prophylaxis and, therefore, were included in the analysis. Of the more than 38 million patients who met these criteria, nearly 7.8 million were admitted for a major or minor surgical procedure and 15.2 million were admitted for a medical indication. Not surprisingly, among surgical patients, a large proportion (56% or 4.3 million) were eligible for thromboprophylaxis based on the 2001 ACCP guidelines. Among those patients who were admitted to a hospital for a medical indication, over 7.7 million (51%) were at risk for VTE based on the 2001 ACCP guidelines. In total, nearly 12.1 million hospitalized patients were at substantial risk for VTE and should have received VTE prophylaxis according to the 2001 ACCP guidelines. Given that nearly 1 in 3 hospitalized patients are at risk for VTE, this represents a very significant public health threat. Although these data were derived from a 2003 population sample and the VTE risk assessment and prophylaxis recommendations are based on 2001 guidelines, it is likely that the number of patients who are at risk for VTE and should receive a recommended prophylaxis strategy will continue to increase in the years to come due to the aging of the population, increasing numbers of orthopedic procedures performed each year, and increasing prevalence of heart failure, stroke, and other acute medical illnesses that place patients at risk for VTE. These data reinforce the importance of screening all patients for VTE risk factors at the time of hospital admission.

This study, conducted by the Worcester Venous Thromboembolism Study Group, examined VTE from an outpatient perspective. Specifically, the investigators attempted to quantify the proportion of patients who first experience VTE symptoms in the outpatient setting, determine the prevalence of well-documented risk factors for VTE in the outpatient setting, and ascertain whether the use (or nonuse) of VTE prophylaxis during a recent hospitalization modifies VTE risk. This was a retrospective study in which trained abstractors reviewed the medical records of all residents of Worcester, Massachusetts, who had a health care encounter (inpatient, outpatient, emergency department, or laboratory) coded with any of 34 VTE diagnostic codes in 1999, 2001, and 2003. Information gathered included patient demographics, history of previous VTE, results of clinical laboratory and diagnostic tests, surgeries, hospitalizations, and use of VTE prophylaxis during previous hospitalizations.

From 7222 potential cases identified in the study periods, 1897 Worcester residents had an independently validated DVT, pulmonary embolism, or both. Of these, 1399 (73.7% of all VTE) were considered cases that occurred in the outpatient setting. More than 40% of the patients had been hospitalized (36.8%) or had major surgery (23.1%) in the 3 months before the VTE. Furthermore, a substantial percentage had a diagnosis of active malignancy (29%) or a history of VTE (19.9%). In those cases in which the VTE was preceded by a hospitalization, more than two thirds presented within 30 days of hospital discharge and more than 40% received no VTE prophylaxis (pharmacologic or mechanical) during the previous hospital stay. The lack of VTE prophylaxis during the previous hospital stay was equally striking among patients with well-known and powerful risk factors for VTE such as surgery (38%), malignancy (36%), or history of VTE (26%).

These data confirm that most DVTs and pulmonary embolisms develop in patients who are not hospitalized, but these events are often temporally related to a hospitalization. Moreover, patients with malignancy or previous VTE are disproportionately represented in this population; therefore, an effective strategy to lower the risk of VTE in the outpatient setting must be targeted to these populations. A significant percentage of patients with strong VTE risk factors did not receive any form of prophylaxis during their hospital stays, and this may have led to
potentially preventable cases of VTE. However, most patients who were previously hospitalized did receive VTE prophylaxis—an observation that suggests that extended prophylaxis after hospital discharge might be a worthwhile strategy in more patient populations.

General Surgery


This meta-analysis sought to expand earlier observations that showed that prophylaxis with LMWH compared with placebo was associated with a reduction in risk of symptomatic DVT, pulmonary embolism, and mortality. The stated objectives of this meta-analysis were to confirm or refute these past findings, but also to evaluate comparative effects of LMWH and UFH in patients undergoing general surgery or surgery for cancer. In addition, the efficacy and safety of low and high prophylactic doses of LMWH were evaluated. Studies included in this analysis were all randomized comparisons of a prophylactic regimen of an LMWH with any other prophylactic strategy in patients undergoing general surgery (defined as abdominal, thoracic, gynecologic, or surgery for malignant disease). Primary and secondary end points were frequency of objectively detected DVT and symptomatic pulmonary embolism, symptomatic VTE, death, major hemorrhage, wound hematoma, other hemorrhage, and postoperative transfusion. Both the number of studies (59) and patients (54,144) included in this meta-analysis were considerable. Unfortunately, the number of different LMWH compounds was also large (nadroparin, certoparin, dalteparin, enoxaparin, parnaparin, and tinzaparin), and as a consequence, it was not possible to compare their relative effects. Low-dose LMWH was defined as 3400 or fewer antifactor Xa U/day, which corresponds to an enoxaparin dose of approximately 35 mg/day.

Compared with placebo or no treatment, use of LMWH was associated with an overall 72% relative risk reduction (RRR) for DVT, a 75% RRR for pulmonary embolism, a 71% RRR for VTE, and a 46% RRR in mortality. All of these differences were statistically significant (p value range 0.001–0.018) except for overall mortality (p=0.09). Failure to achieve statistical significance for mortality was most likely due to the small number of studies (eight) included and the resultant large confidence interval (CI). When compared with UFH, LMWH did not result in statistically significant reductions in DVT, pulmonary embolism, or death (p value range 0.10–0.63), although reduction in VTE did reach marginal significance (p=0.049). Also, when only double-blind studies were considered, none of these achieved statistical significance. In these studies, the dose of UFH was either 5000 U twice/day (30 studies), 5000 U 3 times/day (20 studies), or 2500 U/day (one study). In spite of the substantial number of studies included in this portion of the analysis, no attempt was made to compare the different dosages of UFH. When only cancer surgery was considered, no significant difference could be detected between LMWH and UFH. Finally, no significant difference was observed in the occurrence of clinical events when low-dose or high-dose LMWH was compared with UFH. However, use of low-dose LMWH was associated with a significant 24% RRR of major hemorrhage. Overall, this meta-analysis confirmed earlier observations that prophylactic use of LMWH is clearly effective at preventing clinically important VTE events.


This meta-analysis may be considered supplementary to the one just discussed; although, it assessed different end points and included patients who had undergone orthopedic surgeries. It analyzed randomized, double-blind clinical trials comparing thromboprophylactic efficacy of LMWH and UFH after general and orthopedic surgeries. The primary end points were objectively determined DVT and wound hematoma. Frequency of pulmonary embolism and other categories of major bleeding were included under additional analyses. A total of 36 trials involving 16,583 patients were included in the final analysis. Although there were fewer trials and patients included in this meta-analysis compared with the meta-analysis discussed above (51 and 48,624), observations regarding comparative frequency of DVT between LMWH and UFH were similar in both analyses. Specifically, no significant difference was observed in either analysis in comparative frequency of DVT.
significant 39% reduction in frequency of pulmonary embolism in patients receiving LMWH, whereas in the former analysis only a 12% reduction was observed and it was not statistically significant. Also in this analysis, overall frequency of wound hematoma and other indexes of major hemorrhage were similar in the two treatment groups, observations also noted in the former meta-analysis. Finally, both analyses were unable to demonstrate therapeutic superiority of high-dose LMWH (defined as >3400 antifactor Xa U/day) over either its low-dose counterpart or UFH with respect to DVT. In both studies, however, there was an advantage in using low-dose LMWH with respect to occurrence of bleeding.


This was one of the very early studies that documented the usefulness of subcutaneous LMWH compared with low-dose UFH 5000 U subcutaneously twice/day for prevention of postoperative DVT. As such, it is primarily of historical importance. In this double-blind study, 432 consecutive patients from four centers in Sweden were randomly assigned in blocks of 10 to receive either subcutaneous LMWH, described as “heparin fragment,” or UFH for thrombo-prophylaxis. To preserve the double-blind design, patients assigned to the LMWH group received a subcutaneous placebo injection as their evening dose. Each patient was administered the initial dose 2 hours before scheduled surgery and every 12 hours thereafter for 5–7 days. Preparation of the LMWH was described, and the resultant compound was reported to have a 4:1 ratio of antifactor Xa:antifactor IIa, which is comparable to today’s enoxaparin. The dosage of LMWH administered was reported as 5000 antifactor Xa U/day, a dosage greater than that used today, which is typically 75–3500 U/day. The dosage of UFH administered was the classic 5000 U twice/day. After 30 days of follow-up, the frequency of objectively detected DVT in the LMWH and UFH groups was 4.3% and 6.4%, respectively, (p=0.05), and no significant difference was observed in overall mortality (data and p value not reported). However, the overall frequency of hemorrhagic events was greater in the LMWH group than the UFH group (11.6% vs 4.6%, p=0.007), an observation most likely due to the relatively high dose of LMWH used in this study. There was no assessment of the occurrence of any other VTE events such as pulmonary embolism. The equivalent effect on mortality, however, suggests that pulmonary embolism occurred equally frequently in the two study groups. Since publication of this trial, subsequent comparisons of prophylactic doses of UFH and LMWH have revealed minimal to no differences in the frequency of hemorrhagic complications in patients undergoing general surgery.


Observations from this well-conducted meta-analysis have been used as part of the rationale for identifying DVT prophylaxis as a Medicare quality measure. One strength of this article is that the frequency of specified bleeding complications was analyzed based on the administered dose of LMWH or UFH, and both were compared with placebo. The bleeding complications assessed were injection site bruising, wound hematoma, drain site bleeding, hematuria, gastrointestinal tract bleeding, retroperitoneal bleeding, discontinuation of prophylaxis, and surgery to correct bleeding. Thirty-three randomized control trials involving 33,813 patients were included in this analysis. High-dose LMWH was defined as more than 3400 antifactor Xa U/day, and high-dose UFH was defined as 5000 U 3 times/day.

The two most common bleeding complications were injection site bruising (6.9%) and wound hematomas (5.7%). Not unexpectedly, these complications were observed less frequently in patients receiving placebo (2.8% and 0.8%, respectively). Of note, these bleeding complications were observed more frequently in the low-dose LMWH group than in the high-dose counterparts (bruising 6.8% vs 3.4%, p=0.04, and hematuria 6.6% vs 4.0%, p<0.001). Drain site bleeding, hematuria, and discontinuation of DVT prophylaxis were observed less frequently (2.0%, 1.6%, and 2.0%, respectively). Of note, hematuria was observed considerably more frequently in both high-dose LMWH and UFH groups compared with the low-dose group (5.8% vs 0.4% and 4.7% vs 0.2%, respectively, p<0.001 for both). Finally, rates of the major bleeding complications—gastrointestinal bleeding,
retroperitoneal bleeding, and surgery for bleeding—were all very low (0.2%, 0.08%, and 0.7%, respectively). Based on these observations, it was concluded that pharmacologic thromboprophylaxis was safe for patients undergoing general surgery who are at moderate or high risk for developing DVT. Unfortunately, this conclusion is incompletely supported by the data since there was no assessment of level of patient risk in the 33 studies included in this analysis.


Before publication of this article, efficacy of pharmacologic prophylaxis had been well established for DVT, but mortality, particularly fatal pulmonary embolism, had not been considered fully. The purpose of this well-designed, large clinical trial was to assess the frequency of overall mortality and fatal pulmonary embolism associated with thromboprophylaxis with an LMWH or UFH. In this double-blind study, 23,078 patients enrolled at 67 centers in Germany, Austria, and the Czech Republic were randomly assigned in a double-blind manner to receive either certoparin 3000 antifactor Xa U once/day or UFH 5000 U 3 times/day, both administered subcutaneously. Patients assigned to the certoparin group also received two placebo injections/day in order to preserve the double-blind design of the study. The first dose was given 2 hours before surgery and continued for 5–20 days thereafter. The primary end point was autopsy-confirmed pulmonary embolism occurring during therapy and up to 14 days thereafter. All-cause mortality was the secondary end point and was recorded for the same time period. Data were presented and analyzed in an intent-to-treat manner only.

All-cause mortality was reported as 1.66% in the LMWH group and 1.46% in the UFH group (p=0.28). Autopsy was performed in 70.2% of these patients, and pulmonary embolism was found in 0.15% of patients of both groups (p=0.87). If these latter data were to be extrapolated to the entire cohort of patients, it was estimated that the final rate of fatal pulmonary embolism would have been 0.2%.

Overall, observations of this study revealed that LMWH and UFH were equivalent in prevention of fatal pulmonary embolism and all-cause mortality. The certoparin dosage of 3000 antifactor Xa U/day was somewhat less than the traditionally used LMWH dosage of 3400 antifactor Xa U/day. Such a difference likely had only minimal impact on the outcomes, however, as previous observations with a higher dose of certoparin (5000 antifactor Xa U/day) revealed “no differential efficacy” when compared with the lower dose.

Of note, the highest rates of fatal pulmonary embolism and all-cause mortality were observed in patients who underwent surgery for hip fracture. The authors commented that the benefits of thromboprophylaxis appeared to be blunted in this group of patients.


Before publication of this trial, there had been a number of clinical trials comparing thromboprophylactic efficacy and safety of fondaparinux and enoxaparin after orthopedic surgeries. This was the first trial, to our knowledge, to similarly evaluate fondaparinux and dalteparin after abdominal surgery. In this trial, 2927 patients from 131 hospitals in 22 European counties were randomly assigned in a double-blind fashion to receive either fondaparinux 2.5 mg/day or dalteparin 5000 IU/day, both administered subcutaneously. First doses of fondaparinux and dalteparin were administered 6 hours after surgical closure and 2 hours before surgery, respectively, and double-blind therapy continued for 5–9 days. The primary efficacy outcome was objectively detected VTE (asymptomatic and/or symptomatic DVT and/or pulmonary embolism). The primary safety outcome was major bleeding defined as fatal, retroperitoneal, intracranial, intraspinal, or involving any other critical organ, and bleeding leading to surgery or other interventions such as need for transfusion.

Notably, the trial was originally intended to demonstrate superiority of fondaparinux over dalteparin. The overall rate of VTE, however, was less than anticipated, and a noninferiority analysis was used instead. A VTE was detected in 4.6% and 6.1% of patients in the fondaparinux and dalteparin groups, respectively; a statistically nonsignificant difference that met prespecified noninferiority criteria. Likewise, DVT was observed in 4.2% and 5.8%, respectively.
(p=0.10), and frequency of pulmonary embolism was nearly equal in both groups (0.3% and 0.2%, respectively, statistical analysis not reported). Major bleeding was noted in 3.4% and 2.4% of patients, respectively (p=0.122). Results of previous studies with fondaparinux revealed a clear superiority when compared with enoxaparin for prevention of postoperative VTE in patients who underwent orthopedic surgeries. In this study, fondaparinux was essentially equivalent to dalteparin for the prevention of VTE after major abdominal surgery. It is noteworthy that this effective equivalence was achieved by using a postoperative administration strategy for fondaparinux, which is preferred by many surgeons.

Orthopedic Surgery


Although contrast dye–enhanced venography is commonly used to compare the efficacy of various thromboprophylactic options in patients undergoing major orthopedic surgery, the true relationship between asymptomatic DVT and symptomatic VTE is unclear. This article describes the relationship between asymptomatic DVT and symptomatic VTE in patients undergoing elective hip or knee surgery who were treated with enoxaparin 30 mg twice/day or 40 mg once/day. The frequency of asymptomatic DVT in 10 studies in which venography was performed (5796 patients) was compared with the frequency of symptomatic VTE in two studies in which venography was not performed (3500 patients). The frequency of asymptomatic DVT after total hip replacement (THR) was 13.2% (95% CI 12.2–14.2%) and after total knee replacement (TKR) was 38.1% (95% CI 35.5–40.8%). The 90-day rate of symptomatic VTE after THR was 2.7% (95% CI 2.1–3.4%) and after TKR was 1.8% (95% CI 0.9–2.7%). The asymptomatic venographic DVT:symptomatic VTE ratio was 5:1 in patients undergoing THR and 21:1 for patients undergoing TKR. Despite some differences in the relationship due to the type of surgery and the venogram reading committee, a consistent relationship was found between asymptomatic DVT and symptomatic VTE. The results of this study further strengthen the evidence that DVT detected by means of venography is a valid end point and surrogate for symptomatic VTE.


Although antiplatelet therapy has been shown to be effective in reducing the risk of arterial thrombotic events, controversy exists regarding the role and efficacy of aspirin as a primary thromboprophylactic agent against VTE in patients undergoing major orthopedic surgery. The Pulmonary Embolism Prevention (PEP) trial randomly assigned 13,356 patients undergoing hip fracture surgery and 4088 patients undergoing elective THR or TKR to receive aspirin 160 mg/day or placebo, which was started preoperatively and continued for 35 days. In the hip fracture surgery group, aspirin-treated patients showed a 43% proportional reduction in pulmonary embolism (95% CI 18–60%, p=0.002) and a 29% reduction in symptomatic DVT (95% CI 3–48%, p=0.03). In the elective arthroplasty group, rates of VTE were lower (1.1% in the aspirin group vs 1.4% in the placebo group, hazard ratio (HR) 0.81, 95% CI 0.47–1.42), but the proportional effects of aspirin were similar to those of the hip fracture surgery group. Among all 17,444 randomized patients, the risk of pulmonary embolism or DVT was decreased by 34% (95% CI 17–47%, p=0.0003). Deaths due to bleeding were higher in the aspirin group compared with the placebo group (p=0.04).

This is one of the largest trials that support a role for aspirin as a thromboprophylactic option against VTE in major orthopedic surgery. Although the results suggest that low-dose aspirin is beneficial in reducing the risk of pulmonary embolism and symptomatic DVT in patients undergoing hip fracture surgery and in elective hip or knee arthroplasty, data from previous and often methodologically limited studies are inconclusive and controversial. As more effective methods of prophylaxis are available in patients undergoing major orthopedic surgery, the role of aspirin remains highly controversial. Because of the availability of more effective therapies, the ACCP guidelines recommend against the use of aspirin as a sole thromboprophylactic agent in this patient group.


Preventing VTE in patients undergoing TKR is difficult due to the bleeding risk associated with the procedure and the relative resistance of this procedure to the effect of most traditional antithrombotic agents. This double-blind, randomized, controlled study added to the already existing body of evidence supporting the efficacy and safety of LMWH when compared with warfarin in patients undergoing TKR surgery. Six hundred seventy patients undergoing TKR were randomly assigned to receive enoxaparin 30 mg subcutaneously every 12 hours or adjusted-dose warfarin (INR 2–3), both of which were started after surgery. The rate of DVT in patients with adequate bilateral venograms was the primary end point, and bleeding was the secondary end point.

In the 417 patients with adequate venograms, the rate of DVT was lower in the enoxaparin group compared with the warfarin group (36.9% vs 51.7%, p=0.003), with an absolute risk difference of 14.8% in favor of enoxaparin (95% CI 5.3–24.1%). The rates of proximal DVT and major bleeding were not significantly different between the two groups (p>0.2 for both). This study further confirmed that prophylaxis with an LMWH after TKR resulted in better efficacy outcomes compared with traditional agents such as warfarin and strengthened the role of LMWH as a preferred prophylactic option in these patients. Despite the efficacy benefit that enoxaparin conferred over warfarin, the rate of residual thrombosis was still fairly high in both treatment groups, leaving the quest open for even more effective therapeutic options. The current ACCP guidelines recommend either of these strategies, or fondaparinux, for VTE prevention after TKR surgery.


Both warfarin and LMWH are now part of the accepted drugs available for prophylaxis of VTE in patients undergoing THR. In this randomized, open-label, parallel group study, the efficacy and safety of LMWH (enoxaparin) and warfarin in the prevention of clinically symptomatic VTE was evaluated in patients undergoing THR. The study was divided into two phases: up to 14 days during hospitalization, and a follow-up period of 3 months after discharge. Three thousand eleven patients were randomly assigned to in-hospital treatment with enoxaparin 30 mg subcutaneously every 12 hours to begin within 24 hours of surgery, or adjusted-dose warfarin to begin within 48 hours before surgery to 24 hours after. A total of 1516 patients received enoxaparin, and 1495 received warfarin. Mean duration of treatment with either drug was 7.3 days.

During the entire study period, clinically important VTE occurred in 3.6% (55 patients) of the enoxaparin group and 3.7% (56 patients) of the warfarin group (p=0.8). During hospitalization, four enoxaparin-treated patients (0.3%) and 17 warfarin-treated patients (1.1%) experienced a VTE (p=0.0083). This benefit in the enoxaparin group was lost after therapy was stopped, with no significant difference in VTE between the enoxaparin and warfarin groups at 3 months after discharge (3.4% vs 2.6%, p=0.22). Major or minor bleeding occurred in 152 (10%) enoxaparin-treated patients and in 110 (7.4%) warfarin-treated patients (p value not reported). There was a notable relationship between the timing of the initial enoxaparin dose and major bleeding, as 14 of 18 enoxaparin-treated patients who had a major bleed received the first dose less than 12 hours after surgery. Although this study favors the use of LMWH over warfarin in patients undergoing THR at least for the short term (up to 14 days), it also raises questions about the duration of prophylaxis in these patients.


Similar to patients who undergo TKR and THR, patients undergoing hip fracture surgery are at very high risk for postoperative VTE. This systematic review evaluated the efficacy of UFH, LMWH, and physical methods of prophylaxis in patients undergoing hip fracture surgery. A total of 31 trials involving 2958 patients were included. Compared with the control, UFH and LMWH resulted in a lower rate of DVT (26% vs 42%, RR 0.60, 95% CI 0.5–0.71). Overall mortality was not significantly different between the UFH-LMWH and control groups. Data were insufficient to determine if there was an efficacy or safety difference between UFH and LMWH. Mechanical foot pumping devices offered benefit
over control (7% vs 22%, RR 0.31, 95% CI 0.19–0.51), but the studies evaluating them were limited by methodologic flaws, thus these results have to be interpreted with caution. The influence of various treatments on fatal pulmonary embolism and mortality could not be determined due to insufficient data. This analysis confirms that mechanical foot pumping devices, UFH, and LMWH are effective in the prophylaxis of DVT after hip fracture surgery, but mechanical methods are limited by compliance. Whether there is an efficacy or safety benefit of LMWH over UFH in this patient population is still unclear based on the results of this systematic review. The LMWHs are generally preferred in practice mainly because of convenience.


This meta-analysis of randomized, controlled studies was conducted to better assess the place in therapy of adjusted-dose vitamin K antagonists among the other available VTE thromboprophylactic strategies in patients undergoing major orthopedic surgery. The use of vitamin K antagonists was found to be more effective than placebo or no treatment in reducing DVT (567 patients, RR 0.56, 95% CI 0.37–0.84, p<0.01) and clinical pulmonary embolism (651 patients, RR 0.23, 95% CI 0.09–0.59, p<0.01) but was associated with a higher rate of wound hematoma (162 patients, RR 2.91, 95% CI 1.09–7.75, p=0.03). Vitamin K antagonists were also more effective than IPC in preventing proximal DVT (534 patients, RR 0.46, 95% CI 0.25–0.82, p=0.009). The benefit:risk ratio of vitamin K antagonists was comparable to that of UFH and antiplatelet agents, but the number of studies comparing these options was low. Compared with LMWH, vitamin K antagonists were less effective in preventing total DVT (9822 patients, RR 1.51, 95% CI 1.27–1.79, p<0.001) and proximal DVT (6131 patients, RR 1.51, 95% CI 1.04–2.17, p=0.028). No significant differences in clinical pulmonary embolism, major bleeding, and wound hematoma were found between LMWH and vitamin K antagonists. The type of surgery (THR vs TKR) or the timing of administration of LMWH relative to surgery (pre- vs postoperative) did not have a significant effect on the results. As both vitamin K antagonists and LMWHs are common VTE prophylactic options in patients undergoing major orthopedic surgery, the data from this analysis tips the balance in favor of LMWHs in this population.


The ACCP guidelines support both LMWH and warfarin as appropriate prophylactic options against VTE in patients undergoing THR. In addition to efficacy and safety considerations, cost-effectiveness of available therapies is often a factor in agent selection. This article provides a decision-analysis model in a hypothetical cohort of 10,000 patients undergoing THR in a study that compared a prophylactic strategy of warfarin, enoxaparin, and no prophylaxis. For each strategy, estimates were derived from data in the literature on expected cases of DVT, pulmonary embolism, and deaths, as well as costs of VTE care. Compared with no prophylaxis, warfarin was estimated to reduce DVTs from 1000 to 420/10,000 patients and deaths due to VTE from 250 to 110/10,000 patients. The cost of care for DVT was estimated to be reduced from $530 to $330/patient with warfarin. Prophylaxis with enoxaparin was estimated to further reduce the rate of DVT and related mortality (250 and 70/10,000 patients, respectively), but increase costs by $50/patient treated. Still, enoxaparin would offer an overall cost benefit over warfarin by $12,000/death avoided. Although the acquisition cost of enoxaparin is higher than that of warfarin, it appears to be cost-effective when used for prophylaxis in patients undergoing THR, at least based on the estimates used in this analysis.


This is one of the landmark studies describing the frequency and time course of clinical VTE after THR and TKR. Patients with a diagnosis of DVT or pulmonary embolism within 3 months of a THR or TKR surgery were identified from a State of California–linked hospital discharge database. The cumulative frequency of DVT or pulmonary embolism within 3 months of surgery was 2.8% after THR (556/19,586 cases) and 2.1% after TKR (508/24,059 cases, difference 0.7%,
95% CI 0.4–1.0%). These rates are lower than the 30–45% rate of VTE reported in studies that used screening venography and indicate that in most cases VTE resolves without causing symptoms that patients would perceive as significant enough to seek further care. The major finding of the study was that VTE was diagnosed after hospital discharge in 76% of patients who underwent THR and 47% of those who had TKR (difference 29%, 95% CI 23–34%, p<0.001), raising the question of needing to extend prophylaxis beyond hospital discharge. The median time to diagnosis of VTE was longer in the THR than the TKR group (17 vs 7 days, p<0.001). The type and duration of thrombo-prophylaxis used was identical in the THR and TKR groups, with 95% of cases receiving prophylaxis. Based on these findings, a shorter but more aggressive course of prophylaxis should be used in patients undergoing TKR, whereas those undergoing THR need a longer course of therapy. The findings of this study are significant in that they allow clinicians to further define the appropriate duration of prophylaxis in patients undergoing THR or TKR surgery.


This meta-analysis evaluated the efficacy of extended-duration out-of-hospital prophylaxis on symptomatic VTE after THR and TKR surgery. Nine studies (3999 patients) were included: eight used LMWH and one used UFH. The frequency of symptomatic VTE was significantly reduced in patients receiving extended prophylaxis for 30–42 days versus those whose prophylaxis was stopped at hospital discharge (1.3% vs 3.3%, OR 0.38, 95% CI 0.24–0.61). The reduction in VTE was greater in the THR group (1.4% vs 4.3%, OR 0.33, 95% CI 0.19–0.56) compared with those who underwent TKR (1.0% vs 1.4%, OR 0.74, 95% CI 0.26–2.15). The rate of major bleeding was not affected, but there was an increase in the rate of minor bleeding associated with extended prophylaxis (3.7% vs 2.5%, OR 1.56, 95% CI 1.08–2.26).

The results of this study support that by extending prophylaxis with LMWH or UFH beyond hospital discharge in patients undergoing THR and TKR surgery, the significant reduction in symptomatic VTE events is equivalent to a RR of 20 events/1000 patients treated. Consistent with findings from previous studies, this meta-analysis also suggests that an extended duration of prophylaxis may be less effective in patients undergoing TKR compared with those undergoing THR. Unlike previous studies that raised questions about the clinical relevance of asymptomatic DVT and its link to symptomatic events, this analysis showed that a reduction in symptomatic thrombosis was also paralleled by a similar decrease in asymptomatic events. These findings help support the link between asymptomatic and symptomatic DVT and that asymptomatic clots detected with venography can be used as a surrogate marker for symptomatic events.


Clinical practice differences exist between European and North American countries with regard to timing of initiation of LMWH preoperatively or postoperatively in patients undergoing major orthopedic surgery. Preoperative initiation of prophylaxis is based on the premise that DVT starts during surgery and the aim is to optimize anticoagulant efficacy, whereas postoperative initiation is usually performed 12–24 hours after surgery with the aim of minimizing the risk of bleeding. This meta-analysis sought to analyze efficacy and safety outcomes between preoperative and postoperative initiation of LMWH (enoxaparin) prophylaxis in patients undergoing THR surgery. Included trials were selected by strict criteria, including double-blind design, DVT documentation by contrast-enhanced venography performed before or at the time of hospital discharge, and the use of the enoxaparin started either before or after surgery in doses previously shown to be effective. The authors found that preoperative initiation of enoxaparin was more effective than postoperative initiation, with a DVT frequency of 10% versus 15.3% (p=0.02). Major bleeding was also less frequent in patients in whom enoxaparin was started preoperatively compared with those in whom therapy was started postoperatively (0.9% vs 3.5%, p=0.01).

The findings of this meta-analysis support the view that optimal protection against DVT induced by surgery is attained by preoperative initiation of prophylaxis. These findings were rather surprising, as typical clinical practice in
the United States was to begin thromboprophylaxis with LMWH postoperatively in patients undergoing major orthopedic surgery. The results of this meta-analysis were viewed as hypothesis generating and led to the evaluation of this same clinical question in subsequent randomized clinical trials.


As clinical practice patterns differ with regard to the timing of initiation of LMWH prophylaxis in patients undergoing major orthopedic surgery, this study sought to elucidate the timing for start of prophylaxis that will maximize treatment efficacy. A “just-in-time” concept was applied that would clarify the right balance between immediate pre- or postoperative treatment initiation and bleeding. This was a double-blind, randomized trial that evaluated three different treatment approaches: dalteparin 2500 IU started within 2 hours before surgery and a second dose given at least 4 hours after surgery, then 5000 IU/day; dalteparin 2500 IU given at least 4 hours after surgery, then 5000 IU/day; or warfarin once/day (goal INR 2–3) started on the evening after surgery. A total of 1472 patients undergoing THR were enrolled. The primary end point was DVT detected by contrast-enhanced venography after surgery (mean 5.7 days). The rates of DVT in the groups receiving preoperative or postoperative dalteparin or warfarin for all DVT were 10.7%, 13.1%, and 24%, respectively (p<0.001 for both pre- and postoperative dalteparin vs warfarin). The rates of proximal DVT were 0.8%, 0.8%, and 3%, respectively (p=0.04 and p=0.03 for pre- and postoperative dalteparin vs warfarin). The RRR ranged from 45–72% in favor of the dalteparin groups compared with warfarin. The frequency of major bleeding was higher in the preoperative dalteparin group compared with warfarin (p=0.01).

This study demonstrates that dalteparin when started in close proximity to surgery either before or after surgery results in better efficacy outcomes than warfarin in patients undergoing THR surgery. As both warfarin and LMWH are recommended prophylactic options according to the ACCP guidelines, this study demonstrated that further efficacy benefit can be gained with LMWH compared with warfarin if the timing of LMWH therapy initiation is in close proximity to surgery (mean ± SD 6.6 ± 2.4 hrs). In addition, this was the first major study to demonstrate improved efficacy in the prevention of proximal DVT with an LMWH compared with warfarin. This finding was in contrast to results of studies that used 12–24-hour postoperative initiation of LMWH and that failed to show a significant benefit compared with oral anticoagulants. The results of this study confirmed the role of the just-in-time or close-to-surgery initiation of anticoagulant agents, and all major studies evaluating new anticoagulant agents are now following this strategy to maximize anticoagulant efficacy.


Despite the new knowledge gained regarding the appropriate timing of LMWH after THR, the translation of the just-in-time or close-to-surgery initiation of prophylaxis to clinical practice is still lagging behind in the United States. At the time this report was published in 2001, standard practice was still a delayed initiation of LMWH at 12–24 hours after surgery. This systematic review was conducted to assess the efficacy and safety of LMWH started at different times in relation to surgery compared with oral anticoagulation. Four trials met the predefined inclusion criteria. The results showed that LMWH started in close proximity to surgery resulted in an absolute RR of 11–13%, and an RRR of 43–55% for DVT, compared with oral anticoagulation. Initiation of LMWH 12 hours before surgery or 12–24 hours after surgery was not more effective than oral anticoagulation. When LMWH was started at half the usual dose in close proximity to surgery, the rate of clinical or major bleeding was not significantly affected (p=0.16). The results of this systematic review confirmed that appropriate timing of LMWH in relation to major orthopedic surgery is key in maximizing anticoagulant efficacy. Close-to-surgery initiation of LMWH (4–6 hrs after surgery) is now supported by the ACCP guidelines. Delaying initiation of LMWH to 12–24 hours after major orthopedic surgery results in suboptimal efficacy without gaining a major safety advantage, and this practice should be discouraged.

Because of a high residual VTE rate after TKR, the quest for new and more effective anticoagulants continues. Fondaparinux, an indirect synthetic factor Xa inhibitor, was evaluated in this study. A total of 1049 patients undergoing TKR surgery were randomly assigned in a double-blind fashion to receive fondaparinux 2.5 mg/day subcutaneously or enoxaparin 30 mg subcutaneously twice/day. Both treatments were started postoperatively, with enoxaparin started 12–24 hours after surgery and fondaparinux started a mean±SD of 6±2 hours after surgery. The primary efficacy outcome was VTE (DVT detected with venography, documented symptomatic DVT, or documented symptomatic pulmonary embolism) up to postoperative day 11, and the primary safety outcome was major bleeding. The frequency of VTE was significantly lower in the fondaparinux group (12.5% , 45/361) compared with the enoxaparin group (27.8% , 101/363), with an RRR of 55.2% (95% CI 36.2–70.2, p<0.001). The frequency of symptomatic VTE was not significantly different between the two groups, nor was the frequency of death or clinically relevant bleeding. Because of planned regional anesthesia, only 25.6% of enoxaparin-treated patients received the preoperative dose, indicating the difficulty of giving an LMWH dose before surgery in patients undergoing hip fracture surgery.

This study is the second in a series of studies that evaluated the efficacy of fondaparinux in patients undergoing major orthopedic surgery, in this case THR surgery. A total of 2275 patients were randomly assigned to receive fondaparinux 2.5 mg/day subcutaneously started postoperatively or enoxaparin 40 mg/day subcutaneously started preoperatively for at least 5 days. The primary efficacy outcome was VTE (DVT detected with venography, documented symptomatic DVT, or documented symptomatic pulmonary embolism) up to postoperative day 11, and the primary safety outcome was major bleeding and mortality from all causes. The duration of follow-up was 6 weeks.

The frequency of VTE was significantly lower in the fondaparinux group (8.3% , 52/626) compared with the enoxaparin group (19.1% , 119/624), with an RRR of 56.4% (95% CI 39.0–70.3%, p<0.001). The frequency of symptomatic VTE was not significantly different between the two groups, nor was the frequency of death or clinically relevant bleeding. Because of planned regional anesthesia, only 25.6% of enoxaparin-treated patients received the preoperative dose, indicating the difficulty of giving an LMWH dose before surgery in patients undergoing hip fracture surgery. Fondaparinux was found to be more effective than enoxaparin in hip fracture surgery and without an increase in major bleeding. The results of this study contributed to the ACCP guidelines recognizing and categorizing fondaparinux as the preferred agent in hip fracture surgery (grade 1A recommendation), as data with warfarin and LMWH are limited.


This is the third in a series of four studies that evaluated the efficacy and safety of fondaparinux in major orthopedic surgery, in this case THR surgery. A total of 2275 patients were randomly assigned in a double-blind fashion to receive fondaparinux 2.5 mg/day subcutaneously or enoxaparin 30 mg subcutaneously twice/day. Both treatments were started postoperatively, with enoxaparin started at 12–24 hours after surgery and fondaparinux started a mean±SD of 6±2 hours after surgery. The primary efficacy outcome was VTE (DVT detected with venography, documented symptomatic DVT, or documented symptomatic pulmonary embolism) up to postoperative day 11, with the primary safety outcome being a composite of major
bleeding and death.

The rate of VTE was 6% in the fondaparinux group (48/787) compared with 8% in the enoxaparin group (66/797) with an RRR of 26.3% (95% CI -10.8–52.8%, p=0.099). The frequency of symptomatic VTE was lower in the enoxaparin group compared with that in the fondaparinux group (0.1% vs 1%, 95% CI -0.0–1.9%, p=0.006). The frequency of major bleeding or death was not significantly different between the two groups. In this study, once-daily fondaparinux started in close proximity after surgery was not significantly more effective than enoxaparin started 12–24 hours after surgery. Although the reduction in risk of VTE achieved by fondaparinux in this study was not statistically significant, the results of this study are consistent with those of the other three studies in this series, which showed greater efficacy of fondaparinux compared with enoxaparin in TKR, hip fracture, and THR surgeries.


This meta-analysis of four major randomized, double-blind trials in 7344 patients undergoing TKR, THR, or hip fracture surgery was conducted to evaluate whether the efficacy and safety of fondaparinux 2.5 mg/day subcutaneously starting 6 hours after surgery was more effective than and as safe as the approved enoxaparin regimens, started either before or after surgery, in preventing VTE. The primary efficacy outcome was VTE (DVT detected with venography, documented symptomatic DVT, or documented symptomatic pulmonary embolism) up to postoperative day 11, and the primary safety outcome was major bleeding.

The rate of VTE was 6.8% in the fondaparinux group (182/2682) compared with 13.7% in the enoxaparin group (371/2703), with a common odds reduction of 55.2% (95% CI 45.8–63.1%, p<0.001). This effect was consistent across all types of surgery and all subgroups. The occurrence of major bleeding was more frequent in the fondaparinux group (p=0.008), but that of clinically relevant bleeding was not significantly different. Fondaparinux 2.5 mg/day subcutaneously started 6 hours after surgery was found to be more effective than approved doses of enoxaparin in patients undergoing major orthopedic surgery, with an overall risk reduction of greater than 50% but with an increase in major bleeding. These findings have led to fondaparinux being included in current national guideline recommendations as a grade 1A therapeutic option along with LMWH and warfarin in patients undergoing major orthopedic surgery.

Central Nervous System Procedures and Injuries


When this article was published, little was know about the most appropriate method of prophylaxis in patients undergoing neurosurgery. Mechanical methods were often primarily used because of perceived established efficacy as well as the lack of bleeding risk. In fact, pharmacologic prophylaxis was often avoided for fear of the potential for intracranial hemorrhage. This study assessed the safety of enoxaparin when added to mechanical methods of VTE prophylaxis for patients undergoing neurosurgery. The authors conducted a multicenter, randomized, double-blind trial in which all patients received GCS. In addition to GCS, patients received either enoxaparin 40 mg/day for at least 7 days or matching placebo injection. Enoxaparin was started at least 24 hours after the end of the surgical procedure. The primary end point was the occurrence of VTE by day 8. Venous thromboembolism was identified either through symptoms and confirmed with venography, or through bilateral venography to identify asymptomatic clots.

Of the 307 patients assigned to treatment groups, 129 (84%) of the 154 patients receiving placebo and 130 (85%) of the 153 patients receiving enoxaparin had venographic studies adequate for analysis. The rate of VTE was lower in patients receiving enoxaparin (17%) compared with those receiving placebo (32%). The RRR with enoxaparin added to GCS was 0.52 (95% CI 0.33–0.82, p=0.004). The rate of proximal DVT was also lower in patients receiving enoxaparin versus placebo (5% vs 13%, p=0.04). Clinical symptomatic VTE events occurred in nine patients receiving placebo and one patient receiving enoxaparin. The frequency of major bleeding did not differ significantly between groups, including the rates of intracranial hemorrhage. Death also occurred at a similar
rate during the 60-day study period. Of importance, this study established that not only was pharmacologic prophylaxis more effective than mechanical prophylaxis with GCS in patients undergoing elective neurosurgery, but also that enoxaparin 40 mg/day could be used safely in this patient population.


As in the study discussed above, the authors noted that although patients undergoing neurosurgery are at an elevated risk for VTE, the optimal method of prophylaxis had yet to be determined. Whereas the preference of neurosurgeons was to use mechanical methods of prophylaxis as they did not evaluate the risk of bleeding, a substantial risk for VTE remained even when these methods were used. Therefore, the authors sought to evaluate the effects of adding an LMWH, in this case nadroparin, to GCS for VTE prophylaxis in patients undergoing neurosurgery. Patients older than 18 years undergoing craniotomy or spinal column surgery were randomly assigned to receive bilateral GCS alone (control group), or the combination of GCS and nadroparin 7500 antifactor Xa U once/day (nadroparin group). Compression stockings were continued until hospital discharge, whereas nadroparin, which was started 18–24 hours after surgery, was continued for 10 days or until hospital discharge, whichever occurred first. Patients were assessed daily for signs and symptoms of VTE and bleeding. In addition, patients underwent ultrasonographic surveillance at 6, 8, and 10 days after surgery, as well as bilateral venography for all patients who had not developed VTE by day 10.

An initial 485 patients were enrolled, but only 166 of the nadroparin group and 174 of the control group had an adequate venogram; thus 340 patients were randomized. A DVT occurred in 18.7% of patients in the nadroparin group and 26.3% of the control group (p=0.047). Proximal DVT was also reduced in the LMWH group compared with the control group, although this did not reach statistical significance (p=0.065). Major bleeding occurred in six patients in the nadroparin group and in two patients in the control group (p=0.087). The reductions in the occurrence of VTE were maintained out to 8 weeks. Of concern was that mortality was increased in the 56-day study in patients receiving nadroparin (9.1% vs 4.1%), although none of the deaths could be attributed to the occurrence of bleeding. Despite the mortality results, this trial adds important information and confirms the results from previous trials that LMWH when used with GCS reduces the occurrence of VTE and can be used safely in patients undergoing neurosurgical procedures.


Although there had been some small investigations regarding the use of low-dose UFH and LMWH for the prevention of VTE in neurosurgery, confidence in the overall safety and efficacy of these agents was still questioned by health care practitioners. The absolute magnitude of benefit of pharmacologic compared with mechanical VTE prophylaxis in patients undergoing neurosurgery was not clear, and concerns remained regarding the risk of bleeding, especially intracranial hemorrhage. Hence, this meta-analysis of controlled, randomized trials on the efficacy and safety of heparins in the prophylaxis of VTE in patients undergoing neurosurgery was performed. Pertinent publications that evaluated either low-dose UFH or LMWH were identified by searching MEDLINE and scanning meeting abstracts, as well as by reviewing references from available systematic reviews. This process identified four controlled, randomized studies, three of which involved LMWH, that met criteria to be included in the analysis. One hundred eighty-seven VTE events (22.6%) were recorded in 827 patients. Prophylaxis with low-dose UFH or LMWH resulted in a 45% RRR in VTE events (OR 0.48, 95% CI 0.35–0.66, p<0.001). No fatal bleeding events were noted, but the use of heparins for prophylaxis did result in a 71% RR increase of major bleeding (OR 1.72, 95% CI 0.69–4.27, p=0.24). The authors noted that the use of heparins for prophylaxis resulted in a number needed to treat of eight to prevent one VTE event, and 16 to prevent one proximal DVT. The number needed to harm was 102. Overall, this meta-analysis confirmed the results of earlier smaller trials that the use of a heparin, primarily LMWH, reduces the occurrence of VTE in patients undergoing neurosurgery. Furthermore, the use of LMWH in this population does not appear to increase the risk of intracranial hemorrhage.

Before the publication of this article, little information was available on whether LMWH could be used safely to prevent VTE events in patients experiencing intracranial hemorrhage secondary to blunt-force trauma. In fact, previous investigations of VTE prophylaxis in trauma patients excluded those who had experienced intracranial hemorrhage. However, patients with trauma who also experience intracranial hemorrhage are at a particularly high risk for VTE, and the ability to use a convenient and effective LMWH regimen would be advantageous. Therefore, the investigators conducted this study to evaluate the safety of early anticoagulation in patients with intracranial hemorrhagic injury. This was a prospective, single-center, observational study evaluating the safety of administering enoxaparin 30 mg subcutaneously twice/day, starting approximately 24 hours after initial evaluation. Important aspects of the protocol included the following: withholding enoxaparin for the first 72 hours in patients with splenic injuries managed without surgery, withholding enoxaparin for 24 hours in patients who underwent craniotomy or cranioplasty, and use of IPC only before the initiation of enoxaparin or during the 24 hours surrounding craniotomy or cranioplasty when enoxaparin was withheld. Enoxaparin was administered for the duration of hospitalization or until a patient met the prespecified exclusion criteria.

During an 18-month period at the study center, 1428 patients were identified as experiencing blunt-force trauma, with 177 patients having a documented intracranial hemorrhagic injury on initial computed tomographic (CT) scan. One hundred fifty of the 177 patients received enoxaparin beginning approximately 24 hours after hospital admission until discharge. Four hundred sixty-eight CT scans were obtained in the study population, with 34 showing progression of intracranial hemorrhagic injury. Twenty-eight of those occurred before initiation of enoxaparin with no further worsening of the injury occurring after initiation of enoxaparin. Six patients showed progression of intracranial hemorrhagic injury after enoxaparin initiation, with the LMWH subsequently being discontinued. All six patients survived hospitalization. No significant differences were noted with respect to bleeding complications between patients who underwent surgery (2/24 [8%]) and those who did not (4/126 [3%]). A DVT was identified in two patients (2%). The authors noted that the rate of bleeding complications was similar to previously reported findings on the rate of bleeding in patients undergoing elective neurosurgery with low-dose UFH as the method of VTE prevention.

This trial added important information regarding whether the use of enoxaparin is safe in patients with intracranial hemorrhagic injury secondary to blunt-force trauma. Many patients undergo the placement of a Greenfield filter to prevent fatal pulmonary embolism when trauma is complicated by an intracranial hemorrhagic injury because of the fear of worsening the hemorrhage. The LMWHs are considered the most effective means of VTE prophylaxis for trauma patients, and the ability to use these agents even in patient with intracranial hemorrhagic injury would likely decrease the risk of both VTE and complications from Greenfield filter placement.


These authors, noting that patients with acute SCI have one of the highest rates of VTE, conducted a prospective, multicenter study comparing low-dose UFH 5000 U subcutaneously every 8 hours plus IPC, with enoxaparin 30 mg subcutaneously twice/day with no IPC during the early phase (first 2 wks) of SCI. Previous investigations had established that mechanical methods were inadequate in this population and that although combining mechanical methods with low-dose UFH improved efficacy, the combination could be considered impractical to implement. Based on previous investigations in orthopedic surgery in which LMWH (enoxaparin) was demonstrated to be superior to low-dose UFH, the authors conducted this study to assess whether LMWH could provide similar or better efficacy than the combination of low-dose UFH plus IPC.

Four hundred seventy-six patients were randomly assigned to receive at least one dose of study drug. From this population, only 107
patients were evaluated for efficacy, as they completed the full course of prophylaxis and underwent adequate proximal and distal venography, had proximal DVT confirmed by duplex ultrasonography, or had clinical evidence of pulmonary embolism. In this evaluation cohort, the frequency of VTE was 63.3% in the UFH plus IPC group versus 65.5% in the enoxaparin group (p=0.81). Rates for proximal pulmonary embolism in 181 patients who underwent at least proximal venography were not statistically significantly different between groups (UFH plus IPC 6.5% vs enoxaparin 9.0%). The frequency of pulmonary embolism was 18.4% in the UFH plus IPC group compared with 5.2% in the enoxaparin group (p=0.03).

All 476 randomized patients were evaluated for safety, and the rate of major bleeding was 5.3% with UFH plus IPC compared with 2.6% in the enoxaparin group (p=0.14). Minor bleeding was reported in 17.9% of the UFH plus IPC–treated patients and in 14.8% of the patients receiving enoxaparin. The authors concluded that in the early treatment phase after SCI, safety and efficacy were generally similar with UFH plus IPC and enoxaparin.

Other relevant analyses from the study include the compliance rate for mechanical devices, as well as risk factors for the development of VTE in this population. Overall, this study was significant in establishing a more feasible regimen of LMWH alone as being as effective and safe as UFH plus IPC in patients in the early phase of SCI. Of importance, although it is reasonable to think that the combination of LMWH and IPC would produce additive effects, the hypothesis would need to be tested in an appropriately designed trial.


Little information was available on the risk of VTE in patients during the rehabilitation phase after SCI. To address this issue, a prospective, multicenter study compared low-dose UFH with enoxaparin for prophylaxis against VTE during the rehabilitation phase after SCI (wks 3–8 after injury). This study was a continuation of the early-phase investigation comparing low-dose UFH 5000 U every 8 hours plus IPC versus enoxaparin. Patients were eligible for the rehabilitation-phase portion if they had completed the early-phase study without objective evidence of VTE. Patients in the rehabilitation phase received the same prophylaxis regimen to which they were randomly assigned in the early phase, except that IPC was discontinued in patients assigned to receive low-dose UFH, and the dosage of enoxaparin was reduced from 30 mg twice/day to 40 mg once/day. Patients who had no clinical symptoms of VTE during the rehabilitation phase subsequently underwent repeat bilateral lower extremity duplex ultrasonography at the end of the study period.

A total of 172 patients completed the early-treatment phase period. Of these, 119 patients completed the rehabilitation phase and had adequate imaging. New VTE was demonstrated in 13 of 60 patients treated with low-dose UFH versus 5 of 59 enoxaparin-treated patients (21.7% vs 8.5%, p=0.052). Patients who received at least one dose of study drug were included in the safety analysis. No major bleeding events occurred in the enoxaparin group and one occurred in the low-dose UFH group. Only one patient from each group was discontinued from the study because of bleeding. Significant observations from this study include the confirmation that patients in the rehabilitation phase of SCI remain at high risk for VTE events, as well as that enoxaparin 40 mg/day appears to be more effective that low-dose UFH 5000 U every 8 hours at preventing VTE.


Previous investigations of the value of LMWH for VTE prophylaxis in patients with acute SCI used enoxaparin 30 mg subcutaneously twice/day. This study was undertaken to evaluate the safety and efficacy of enoxaparin 40 mg subcutaneously once/day compared with the 30-mg twice-daily regimen. Patients receiving either enoxaparin prophylactic regimen were identified through a retrospective chart review over a 2-year period at a single rehabilitation facility. A total of 129 patients with acute SCI received either enoxaparin 40 mg once/day (80 patients) or enoxaparin 30 mg twice/day (49 patients) as the primary mode of VTE prophylaxis. Enoxaparin was started an average of 23.6 days and 20.6 days after SCI for the once- and twice-daily regimens,
respectively. The mean length of prophylaxis with enoxaparin was 42.7 days in the twice-daily regimen group and 39.5 days in the once-daily regimen group. Despite a lack of randomization, the patient groups were similar with respect to general demographics, the level of SCI, and other comorbidities.

Over the duration of prophylaxis, one patient in each group experienced a DVT. One pulmonary embolism occurred during the evaluation period in the twice-daily regimen group. Bleeding complications were numerically higher in the once-daily regimen group (20 vs 5 complications), with the difference not achieving statistical significance. Limitations of the study include the retrospective nature along with the lack of randomization. Although the two groups of patients were well matched with major variables that may serve as confounders, not all confounders can be identified and eliminated in studies of this type. Nevertheless, the results would suggest that enoxaparin 40 mg once/day is as safe and efficacious as a regimen of 30 mg twice/day in patients with SCI. However, given the number of patients assessed in the study, it may have been difficult to detect small differences between the regimens. Advantages with using the once-daily regimen include decreased cost and ease of use in a patient population that may receive prophylaxis for an extended duration. Although the study may provide enough evidence for some to use enoxaparin 40 mg once/day for prophylaxis in patients with SCI, confirmation of these results in a larger randomized trial would be optimal before universal implementation.


This was a retrospective case-control analysis that evaluated the efficacy and safety of dalteparin 5000 IU subcutaneously once/day compared with enoxaparin 30 mg subcutaneously twice/day in patients with either acute SCI or major lower extremity orthopedic trauma. In discussing the rationale for the study, the authors succinctly reviewed literature that described a very elevated risk of proximal DVT and pulmonary embolism in this patient population, and that stated that LMWH is superior to other forms of pharmacologic and mechanical prophylaxis. Most of the published literature discussed enoxaparin. Citing some small published work with dalteparin in these patient populations, the authors implemented an institutional interchange of dalteparin for enoxaparin as the primary mode of prophylaxis. Presumably this switch was made on the basis of equivalent efficacy with reduced cost. The study is an evaluation of the implemented interchange. Despite being a nonrandomized comparison, the groups were well matched with respect to patient characteristics, as well as in hospital events or procedures.

In their analysis, the authors noted that patients had a risk for proximal DVT plus pulmonary embolism of 1.6% with enoxaparin and 9.7% with dalteparin (p=0.103). These results failed to meet the prespecified criteria for noninferiority with the CI crossing the upper boundary of an absolute risk increase of 5%. Bleeding rates were approximately the same, although an interesting finding is that the enoxaparin group had more missed doses, suggesting that once-daily regimens may be easier to comply with.

There are many limitations to this analysis given the retrospective nature of data collection, as well as the absence of statistical methods such as logistic regression to account for confounders between the two groups. However, given the results of this analysis when assessed within the context of other studies using enoxaparin in this patient population, it would seem prudent to operate with the assumption that in acute SCI, enoxaparin 30 mg subcutaneously twice/day should be the preferred strategy since it is well supported by the scientific literature. Given the design of the comparison, it would be misleading to state that enoxaparin 30 mg twice/day is superior to dalteparin 5000 IU once/day. However, given the lack of evidence for dalteparin in VTE prevention for patients with SCI, justifying utilization in this group may be difficult without further investigation.

**Trauma**


The investigators of this meta-analysis included five trials along with 66 patients from their own data that evaluated the efficacy of subcutaneous UFH compared with no prophylaxis
for prevention of VTE in patients with trauma. A total of 1102 patients in this meta-analysis had major trauma (injury severity score > 10) and underwent prospective duplex ultrasonography for DVT. The frequency of VTE in patients receiving UFH was 9.9% compared with 7.2% in patients receiving no prophylaxis (p=0.771). The rate of pulmonary embolism was 1.3% in patients receiving UFH compared with 2.2% in patients receiving no prophylaxis (p=0.157). The rate of bleeding was not reported. Although this meta-analysis includes trials conducted about 15 years ago, the results suggest that subcutaneous UFH is not effective at reducing the risk of VTE in patients with major trauma. The investigators provide a good review of the patients and methods of each of the trials included in the meta-analysis. The dosing of subcutaneous UFH used in the individual trials, however, is not mentioned.


Three hundred forty-four trauma patients in this single-center trial were randomly assigned in a double-blinded fashion to receive UFH 5000 U twice/day or enoxaparin 30 mg twice/day for up to 14 days. Patients in the trial had an injury severity score above 9 and received their first dose of anticoagulant within 36 hours of admission. No additional mechanical prophylaxis was permitted. The primary end point of the trial was the occurrence of venographic DVT, or symptomatic or fatal pulmonary embolism. The use of enoxaparin demonstrated a significant 30% relative reduction in the rate of any DVT (31% vs 44%, p=0.014) and a significant 58% relative reduction in the rate of proximal DVT (6% vs 15%, p=0.012). Major bleeding in these trauma patients occurred rarely and was not significantly different between the groups (five events with enoxaparin vs one event with UFH, p=0.12).

This trial demonstrated improved efficacy of enoxaparin 30 mg twice/day compared with UFH 5000 U twice/day, without an increase in bleeding. Therefore, based on these data, UFH twice/day should not be used in trauma patients, and enoxaparin is preferred. It should be noted that the dosage of enoxaparin is not the typical 40 mg once/day used for VTE prophylaxis in other patient populations. One of the main issues with using pharmacologic VTE prophylaxis in trauma patients is when to start prophylaxis in relation to the risk of bleeding and the extent of the trauma. Patients in this trial had a mean injury severity score of 23, 85% required surgery, and 38% required blood transfusion within the first 24 hours. In that setting, pharmacologic prophylaxis was able to be started within 36 hours of injury, with a significant reduction of DVT and few major bleeding events when enoxaparin 30 mg twice/day was used.


In an attempt to simplify VTE prophylaxis in trauma patients with a once-daily regimen, investigators of this observational trial evaluated 743 trauma patients receiving dalteparin 5000 IU once/day. The patients had a mean injury severity score of 19.5 and length of stay of 14 days; 174 patients had brain injury. On average, patients received 9.2 doses of dalteparin during their hospital stay, but they did not receive their first dose until 3.3 days after injury. The primary end point evaluated was the frequency of ultrasonography-detected DVT. The initial ultrasonographic examination was performed within 48 hours of injury, before prophylaxis was started. Patients with an initial negative ultrasound scan were then included in the trial and reevaluated between days 7 and 10. During the 2 years of study enrollment, 3.9% of patients developed DVT and 0.8% developed pulmonary embolism with no cases of fatal pulmonary embolism. Major bleeding occurred in 2.7% of patients, and 3% required transfusion.

The obvious limitations of this trial are the observational design with no comparator group. Although the authors attempt to state that their results are similar to or even better than the results from the single-center trial discussed above, this conclusion is inappropriate. The single-center trial used a randomized comparison trial design and documented venographic DVT. The use of dalteparin once/day may be a useful option for VTE prophylaxis in trauma patients, but a higher quality trial will be needed to confirm these initial results. The main benefit of this trial to the trauma literature is the finding that pharmacologic VTE prophylaxis does not need to be delayed while waiting for most
KEY ARTICLES FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM Dobesh et al

surgical procedures and does not need to be held before most surgical procedures. Patients in this observational trial had on average five surgical procedures during their hospital stay, and LMWH typically was not withheld.


In this trial, 442 trauma patients were prospectively randomized to subcutaneous enoxaparin 30 mg every 12 hours or IPC. Enoxaparin was started within 24 hours of trauma, but the timing of the initiation of IPC was not provided. The primary end point was proximal DVT detected with duplex ultrasonography and objectively confirmed symptomatic pulmonary embolism. The frequency of the primary end point was 3% with IPC and 0.5% with enoxaparin (p=0.122). Major bleeding was less than 2% in both groups.

Although it may seem that IPC is a reasonable alternative to LMWH for VTE prophylaxis in trauma patients, there are several issues to be considered. First, trauma patients in this study were considered to be at moderate risk since their injury severity score was less than 19 (mean score 17), which is less than that in most of the other trauma VTE prophylaxis trials. It is also unlikely that the trial was powered to find a difference in ultrasonography-detected proximal DVT in moderate-risk patients. Therefore, the 83% relative reduction in VTE in this trial may require further evaluation. The fact that bleeding was similar between the groups demonstrates the safety of LMWH in trauma patients.


The investigators of this cohort trial attempted to answer the important question about timing of initiation of VTE prophylaxis in patients with trauma. Three hundred fifteen patients experienced hemorrhagic shock after their trauma and, therefore, were at high risk for both VTE and bleeding. Pharmacologic VTE prophylaxis was started within 48 hours in 25% of patients and after 7 days in another 25%. Early prophylaxis was defined as starting 4 days or less after trauma (174 patients), and late prophylaxis was defined as starting more than 4 days after trauma (137 patients). Four patients who experienced a DVT within the first 48 hours after admission were excluded from the analysis. Early prophylaxis was associated with a 5% rate of VTE compared with 15% for late prophylaxis (RR 3.0, 95% CI 1.4–6.5). Early prophylaxis was actually associated with significantly less bleeding and need for blood transfusion. This may be because the trial was observational and patients who received “late” prophylaxis were treated in that manner due to their increased risk of bleeding. Although the design of this trial is not optimal, it does provide some insight into the issue of starting pharmacologic prophylaxis as soon as possible to provide maximum protection against VTE.


Both parts I and II of this meta-analysis were conducted by a panel of 17 experts on VTE who represented the academic, private, and managed care sectors. The investigators set out to answer four questions related to prevention of VTE. What is the role of different chemical or mechanical methods in preventing VTE? What are the factors placing trauma patients at high risk for VTE? Which is the optimal method to screen for DVT? What is the role of vena cava filters in preventing pulmonary embolism? This article, which is part I, addressed the first question. Three of the investigators screened 2437 titles, which led to the screening of 225 full articles. Of these articles, 73 randomized, controlled trials were accepted for the meta-analysis.

The rate of DVT and pulmonary embolism varied widely among the trials, with the pooled analysis providing a DVT rate of 11.8% and a pulmonary embolism rate of 1.5%. The dramatic difference in screening methods and reporting in randomized controlled trials made it difficult to have confidence in the accuracy of these findings. Overall, the results of the meta-analysis demonstrated no evidence of efficacy for the use of subcutaneous UFH (OR 0.965, 95% CI 0.353–2.636) or mechanical methods (OR 0.769, 95% CI 0.265–2.236) in the prevention of VTE in trauma patients. The lack of benefit of subcutaneous UFH and mechanical methods was still evident when trials that were not randomized and controlled were added to the analysis of the randomized controlled trials. When evaluating
trials of LMWH, no significant difference was noted in the frequency of pulmonary embolism with LMWH compared with subcutaneous UFH, but the authors mention that the CIs were very wide, and a significant difference cannot be excluded. The use of LMWH was associated with a significant reduction in DVT when compared with subcutaneous UFH, as well as when compared with mechanical prophylaxis, although the data were not presented. The pooled rate of bleeding was 3.6% with subcutaneous UFH and 3.1% with LMWH. The pooled rate of thrombocytopenia was 1.9% with subcutaneous UFH and 0.4% with LMWH. The investigators provide an insightful discussion of the poor quality of randomized controlled trials that evaluated different VTE prophylaxis methods in trauma patients. This meta-analysis represents the best summary of VTE prophylaxis methods in trauma patients in the literature and is frequently referenced in the ACCP guidelines.


This article is part II of the meta-analysis and addresses two of the remaining questions posed by the investigators. The same methods described in part I were used in part II. The only significant risk factors for DVT in trauma patients that were identified were spinal fractures and SCI, which increased the risk by 2- and 3-fold, respectively. Patients with DVT were an average of 9 years older than patients without DVT, but no specific age cutoff point could be determined based on the quality of the trials available. Patients with prophylactic vena cava filters had a rate of pulmonary embolism of 0.2%, whereas the comparator patients without filters in these trials had a rate of pulmonary embolism of 1.5%, and historical controls had a rate of pulmonary embolism of 5.8%. Because of the poor quality of the trials, no statistics were conducted on these findings. These articles provide a broad overview of VTE prophylaxis data in trauma patients and should probably be in the files of clinicians who care for trauma patients in their hospitals.

Intensive Care Setting


This review, by the lead writer of the ACCP section on prevention of VTE, summarizes the risk factors and prevalence of VTE in patients in the intensive care unit (ICU). It builds on an earlier systematic review and examines the few prophylaxis trials using routine, objective screening specifically in patients in the ICU, as well as providing the reader with a simple, practical, individualized approach to prophylaxis in the ICU based on bleeding and thrombosis risk. The review addresses the relevant literature but highlights the lack of robust data specifically derived from the ICU population. Only four prospective studies were identified that used objective testing and reported VTE event rates in intensive care patients not receiving prophylaxis. The overall DVT rate in these four untreated cohorts ranged from 13–31%. One study was a small, prospective, cohort study that used fibrinogen leg scanning for diagnostic testing, whereas the other three were control arms of the only randomized, comparative trials in this arena. In these three studies, one also used fibrinogen leg scanning, and the largest trial was only available in abstract form at the time of this writing. The RRRs with heparin 5000 U subcutaneously twice/day in two of the studies were 55% and 65%, respectively. Unfortunately, neither proximal DVT nor bleeding event rates were reported in either study. The trial that used LMWH showed a 45% RRR but used venography and provided more details. A schematic with specific pharmacologic or mechanical prophylaxis recommendations based on bleeding and thrombosis risk is presented, although details to stratify the bleeding component are not provided. The authors advocate that this assessment occur on admission to the ICU and daily thereafter, and that compliance is enhanced with use of pre-printed orders as well as the active involvement of a pharmacist on daily ICU rounds.


Previous studies have shown efficacy of standard doses of LMWH in trauma patients and have suggested that LMWHs are superior to other methods of VTE prophylaxis in this population. However, it is not clear that standard LMWH doses are optimal in patients in the ICU. This well-written, prospective, observational study of two cohorts of trauma patients clearly illustrates that plasma antifactor Xa concentrations are
highly variable after administration of enoxaparin 30 mg subcutaneously every 12 hours and frequently undetectable in one subset of patients. Strict inclusion and exclusion criteria were used, and the 21 patients evaluated were divided into edema or no edema groups based on whether they had gained at least 10 kg since admission and had peripheral edema at physical examination. No patients were receiving vasopressors at the time of serum antifactor Xa sampling, which took place at multiple time points after at least four enoxaparin doses had been administered to ensure steady state. The cohort with edema, in addition to having a 12-hour area under the concentration-time curve less than half that of the no edema cohort (p=0.01), also had significantly less antithrombin (antifactor IIa) activity (82% vs 66%, p<0.01). This raises the possibility that the reported antifactor Xa levels may overestimate the true in vivo response to LMWH. What remains unanswered is whether clinical outcomes in this arena, or least in those intensive care patients with significant edema, would be enhanced by initial weight-based LMWH dosing and/or adjusting LMWH doses based on target antifactor Xa levels. As more comparative data become available, this study will also serve to clarify if some of the observed variability is a property of the individual drugs studied or more a byproduct of this patient population.


This was a prospective cohort study of 141 consecutive patients admitted to a medical ICU who received DVT prophylaxis according to a risk-stratified protocol and had bilateral lower extremity ultrasonographic examinations performed within 48 hours of admission. An ultrasonographic examination was also performed weekly thereafter, or upon discharge or clinical suspicion of an event. The 801 patients were screened according to preset inclusion and exclusion criteria to arrive at the final cohort. Most (528 patients) were excluded because the anticipated length of medical ICU stay was not greater than 48 hours. The protocol used in this center evaluated for the presence or absence of 10 predetermined risk factors. If 1–3 risk factors were present, the patient was considered at moderate risk and was given subcutaneous UFH, or IPC if UFH was contraindicated. Four or more risk factors resulted in UFH and IPC being used together. An LMWH was not used. The high rate of DVT (9.9%), despite prophylaxis, is fairly consistent with treatment arms of the few previous comparative trials of patients in an ICU. Of note, 10 of the 14 events were proximal DVT, but overall only two of the events were symptomatic. Since 38% of the cohort had contraindications to UFH by their criteria, prophylaxis was fairly evenly distributed between IPC (38%), UFH (32%), and UFH plus IPC (30%). The distribution of DVT did not differ by the type of prophylaxis used. A post hoc analysis of five primary risk factors showed the odds of having a DVT were significantly increased if at least two risk factors were present. Overall this study advances our understanding regarding prophylaxis in the intensive care patient. We await the results of the ongoing Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT), which compares daily LMWH with twice-daily UFH, to further clarify specific prophylaxis recommendations.


Five randomized trials, 13 observational studies, and three surveys were evaluated to form the basis for the rather general recommendations by the ACCP that for critical care patients with high bleeding risk, mechanical prophylaxis should be used until the bleeding risk decreases. Thereafter, pharmacologic prophylaxis can be substituted or added to the mechanical method (GCS and/or IPC). Combining data from the five randomized controlled trials was limited because of the heterogeneity of the patient populations and study methodologies. All patient population types (trauma vs surgical vs medical) were considered but had to be specified for inclusion. Four of the studies involved trauma patients, and of those, only two compared mechanical with pharmacologic (enoxaparin at different doses) prophylaxis. The aggregate rate of DVT detected with ultrasonographic examination on admission and weekly while in the ICU appeared to favor LMWH over IPC (1.4% vs 3.5%) but failed to achieve significance given that only 562 patients were studied.

The authors compiled a complete summary table of observational studies encompassing over 3000 patients, but conclusions were limited.
Three studies evaluated some combination of mechanical compared with pharmacologic prophylaxis and failed to detect a significant difference between the two, but their sample sizes and power to detect a true difference were limited. Survey data highlighted the frequent use of GCS and underscored that practices appeared to vary throughout different worldwide geographic regions. This review is comprehensive but underscores the need for further comparative risk-to-benefit trials involving mechanical prophylaxis, especially in this population often with high clot and high bleeding risks.

Medical Illnesses


This study represents the largest trial ever conducted in medically ill patients. It included 11,693 patients with infectious diseases who were randomly assigned in an unblinded fashion to receive UFH 5000 U every 12 hours until hospital discharge (maximum 21 days) or control. The primary end point of the trial was autopsy-verified pulmonary embolism. No significant difference was noted between the patients receiving UFH twice/day compared with the control group in overall mortality (5.3% vs 5.6%, p=0.39) or autopsy-detected thromboembolic complications (49% vs 49.2%, p=NS). Also, no significant difference was noted in pulmonary embolism or DVT at autopsy. Although the end point of this trial was unique, the trial was adequately powered to find a difference if one existed. Unfractionated heparin 5000 U every 12 hours is a commonly used regimen for prevention of VTE. The results of this large trial suggest that there is no benefit to the use of this regimen in the prevention of VTE in these medically ill patients.


The 100 medically ill patients in this trial had heart failure or chest infection and were randomly assigned to receive UFH 5000 U every 8 hours or control during their hospital stay. The primary end point was the occurrence of DVT detected by fibrinogen scanning. The first scan was obtained within 24 hours of admission, and scanning was repeated every second day for 14 days or until hospital discharge. The rate of DVT was significantly reduced from 26% in the control group to 4% in UFH-treated patients (p<0.01). Hematoma occurred in 20% of patients receiving UFH, but bleeding was not significantly different between groups. Although questions have been raised about the efficacy of UFH 5000 U twice/day for VTE prevention in medically ill patients, this trial demonstrated the efficacy of UFH 5000 U 3 times/day.


Although a twice-daily UFH regimen compared with a thrice-daily UFH regimen for VTE prophylaxis has never been evaluated in a head-to-head comparison trial, both regimens have been compared with another active therapy, placebo, or control. The investigators of this meta-analysis included 12 trials (7978 patients) that compared UFH twice/day (6314 patients) or 3 times/day (1664 patients) with placebo or control for VTE prevention to determine if a difference exists between these two UFH regimens. The rate of any VTE was 5.4% with UFH twice/day and 3.5% with UFH 3 times/day (p=0.87). There was a trend toward lower rates of pulmonary embolism (0.5% vs 1.5%, p=0.09) and lower proximal DVT and pulmonary embolism (0.9% vs 2.3%, p=0.05) with the use of UFH 3 times/daily versus twice/day. The rate of major bleeding was significantly higher in patients receiving UFH 3 times/day compared with twice/day (0.96% vs 0.35%, p<0.001), but the overall risk was very low.

Although clinicians may want to use this meta-analysis as a justification to continue using UFH twice/day, it should be noted that the numeric differences in efficacy from the meta-analysis may be clinically relevant, whereas the difference in major bleeding may not be. Also, there are some limitations to this meta-analysis. First, the method of detection of VTE varied greatly among these trials. The difference in the ability to detect (or prevent) VTE events by using autopsy, venography, ultrasonography, or symptoms makes it difficult to compare these trials. Trials included in this meta-analysis included not only medically ill patients but also critical care
patients, which alters their VTE and bleeding risks compared with typical medically ill patients. Although the information provided by this meta-analysis is interesting, a standard head-to-head comparison trial is needed to completely answer this question.


The Prophylaxis in Medical Patients with Enoxaparin (ME DENOX) trial had two main goals. The first was to evaluate whether medically ill patients were truly at risk for VTE in the current era of medical practice. A number of older trials had reported a VTE rate of about 25%, but medical practice had changed from the time of these older trials to the time of the ME DENOX trial. Therefore, there was a placebo group in the ME DENOX trial. The second goal of the trial was to evaluate the efficacy and safety of two different doses of enoxaparin for VTE prevention, if these patients were at risk. To evaluate these goals, 1102 hospitalized patients older than 40 years were randomly assigned in a double-blind fashion to placebo, enoxaparin 20 mg subcutaneously once/day, or enoxaparin 40 mg subcutaneously once/day. The primary end point of the study was the occurrence of VTE by day 14. Patients were evaluated for VTE by venography if they had a symptomatic event before they went home (average length of stay 7 days) or by day 14, which was the end of the in-hospital follow-up period. Patients were also evaluated 3 months later for the accumulation of any symptomatic events, but not with venography.

Most of the medical illness in the ME DENOX trial consisted of heart failure (33%), acute respiratory failure without a ventilator (53%), acute infectious disease (53%), and acute rheumatic disease (9%). The rate of VTE by day 14 was 14.9% with placebo, 15.0% with enoxaparin 20 mg/day, and 5.5% with enoxaparin 40 mg/day. Proximal DVT by day 14 was 4.9% with placebo, 4.5% with enoxaparin 20 mg/day, and 1.7% with enoxaparin 40 mg/day. Therefore, the ME DENOX trial demonstrated that medically ill patients are at risk for VTE. The VTE event rate of 14.9% with placebo would be defined as a group in the moderate-risk category, but a group of patients who should receive prophylaxis. The trial also demonstrated that enoxaparin 20 mg/day is not effective for prevention of VTE in these patients. Finally, the use of enoxaparin 40 mg/day provides a significant 63% relative reduction in total VTE (p<0.001) and a 65% relative reduction in proximal DVT compared with placebo (p<0.0001 for both comparisons). These significant reductions were still evident at the 3-month follow-up (p<0.001 for both comparisons). The benefits provided by the use of enoxaparin 40 mg/day did not produce an increase in major or minor hemorrhage, but there was a significant increase in the rate of hematoma (0% placebo vs 1.4% enoxaparin 40 mg, p=0.03).


Although the study design of Prospective Evaluation of Dalteparin Efficacy for Prevention for VTE in Immobilized Patients Trial (PREVENT) was similar to that of the ME DENOX trial, the primary end point was different. Instead of evaluating for venographic events, as done in ME DENOX, the PREVENT investigators wanted to evaluate what they defined as “clinically relevant” VTE. The primary end point of the PREVENT trial was the composite of symptomatic distal or proximal DVT, symptomatic or fatal pulmonary embolism, and asymptomatic proximal DVT detected by means of compression ultrasonographic examination at day 21. Since there is controversy about the significance of preventing asymptomatic distal DVT, and the lack of use of venography in clinical practice, the investigators’ definition of clinically relevant VTE seems appropriate. The use of this more difficult end point explains the need for 3 times as many patients in the PREVENT trial compared with that in the ME DENOX trial. The 3706 patients (aged ≥ 40 yrs) in the PREVENT trial were randomly assigned to placebo or dalteparin 5000 IU subcutaneously once/day.

Medical illness in the PREVENT trial consisted of heart failure (52%), acute respiratory failure (30%), acute infectious disease (37%), and rheumatologic disease (11%). Dalteparin provided a significant 45% relative reduction in the primary end point at day 21 compared with placebo (2.77% vs 4.96%, p=0.0015). Proximal DVT was also significantly reduced by 32% with the use of dalteparin compared with placebo (1.79% vs 3.65%). No significant difference was
noted in the rate of hemorrhage between the groups. Hematoma was not evaluated as an independent safety outcome in the PREVENT trial. Therefore, based on the results of the PREVENT trial, dalteparin 5000 IU subcutaneously once/day is an effective and safe option for the prevention of VTE in medically ill patients.


The Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS) investigators sought to evaluate the efficacy and safety of fondaparinux in the prevention of VTE in medically ill patients. The 849 patients with general medical illness who were aged 60 years or older were randomly assigned in a double-blinded fashion to placebo or fondaparinux 2.5 mg subcutaneously once/day. The study design and end points of the trial were similar to those of the MEDENOX trial, with the primary end point being the occurrence of VTE by day 15 detected with venography. Medical illnesses in the ARTEMIS trial consisted of heart failure (25%), acute respiratory disease (20%), and acute infectious or inflammatory disease (25%).

Patients receiving fondaparinux had a significant 47% reduction in VTE compared with patients receiving placebo (5.6% vs 10.5%, p=0.029). The rate of hemorrhage was similar between the groups. As in the PREVENT trial, hematoma was not evaluated as an independent safety outcome. There was an interesting trend toward a reduction in mortality in the ARTEMIS trial (p=0.06). A trend was also suggested in the MEDENOX trial but was not as strong (p=0.31). A much larger trial would be needed to conclude if this possible effect on mortality is real.

The rate of VTE in patients with cancer was 17% in fondaparinux-treated patients compared with 3.9% in placebo-treated patients (p=0.03). Although these data were not in the initial article, it clearly is an odd finding that requires further evaluation.


Several trials have evaluated the efficacy of different anticoagulants for VTE prophylaxis compared with placebo or control in medically ill patients. There is probably no longer a need for placebo-controlled trials for VTE prevention in medically ill patients. These trials consistently demonstrate that medically ill patients are at risk and that providing them pharmacologic prophylaxis reduces that risk. There is now a need for head-to-head comparison trials to determine the optimal regimen for these patients.

The 665 patients in the Thromboembolism–Prevention in Cardiac or Respiratory Disease with Enoxaparin (THE-PRINCE) trial were randomly assigned to either UFH 5000 U 3 times/day or enoxaparin 40 mg once/day. Medically ill patients in THE-PRINCE trial included similar numbers of patients with heart failure or severe respiratory disease. The primary end point of the trial was the occurrence of venography-verified DVT and symptomatic pulmonary embolism up to 1 day after the treatment period (maximum 10 days).

The primary end point occurred in 8.4% of enoxaparin-treated patients compared with 10.4% of UFH-treated patients (p=NS). The use of enoxaparin was associated with fewer adverse events compared with UFH (45.8% vs 53.8%, p=0.44). The THE-PRINCE investigators then separately evaluated efficacy in patients with respiratory disease or heart failure. Since patients with medical illnesses represent a very heterogeneous group, different levels of risk exist. The frequency of the primary end point in patients with respiratory disease was 7.1% for enoxaparin and 5.9% for UFH (p=NS). In the higher risk patients with heart failure, still no significant difference was noted (9.7% enoxaparin vs 16.1% UFH), but clearly the separation of more than 6% requires further study. Therefore, THE-PRINCE investigators’ evaluation of different groups of medically ill patients was quite insightful and set up some of the future research in this area.


This meta-analysis included 36 trials that evaluated the efficacy and safety of UFH, LMWH, or fondaparinux for the prevention of VTE in medically ill patients. Fourteen of the trials evaluated UFH versus control, 11 trials evaluated
LMWH versus control, 10 trials evaluated UFH versus LMWH, and one trial evaluated fondaparinux versus placebo (ARTEMIS). Overall, the use of UFH provided a significant 67% reduction in risk of DVT and a 44% reduction in risk of pulmonary embolism in medically ill patients. The use of UFH 3 times/day (83% risk reduction) was more effective than UFH twice/day (48% risk reduction) in preventing DVT. The use of LMWH was associated with a significant 32% risk reduction of DVT when directly compared with UFH. Neither agent provided a reduction in mortality. Although the risk of major bleeding and thrombocytopenia were not significantly different between UFH and LMWH, there was a significant 53% reduction in risk of injection site hematoma for patients receiving LMWH compared with UFH. At least two additional meta-analyses have evaluated the efficacy and safety of VTE prevention in medically ill patients. Although the methods of these other meta-analyses vary somewhat, the overall conclusions of the benefits and safety of VTE prophylaxis in medically ill patients are similar.


Patients with ischemic stroke represent not only a group of medically ill patients at high risk for VTE, but also a group of patients in whom concern about bleeding is significant. The 1762 patients with acute ischemic stroke in the Prevention of Venous Thromboembolism After Acute Ischaemic Stroke (PREVAIL) trial were randomly assigned in an unblinded fashion to receive enoxaparin 40 mg once/day or UFH 5000 U twice/day for up to 10 days. The primary end point of the trial was venography-confirmed DVT, or symptomatic or fatal pulmonary embolism.

Patients receiving enoxaparin demonstrated a 43% relative reduction in VTE compared with UFH (10% vs 18%, p=0.0001). The rates of any bleeding (8% in both groups) and intracranial hemorrhage (1% in both groups) were not different between the groups. The rate of extracranial bleeding was higher with the use of enoxaparin than with UFH, but the number of overall events was small (seven vs zero events, p=0.015). Although smaller trials have demonstrated a benefit of enoxaparin over UFH, these trials were not large enough to evaluate safety. A limitation of the PREVAIL trial was the use of UFH twice/day compared with 3 times/day. Smaller trials had already demonstrated a benefit of enoxaparin over UFH 3 times/day. The investigators noted the concern of possible increased hemorrhagic transformation with UFH 3 times/day. Therefore, the UFH twice-daily regimen could explain the lower rate of extracranial bleeding compared with that of the enoxaparin regimen, but it probably does not explain the decreased efficacy.


The investigators of this meta-analysis included three trials that evaluated an LMWH compared with UFH for VTE prevention in patients with ischemic stroke. Two of the trials used enoxaparin, and one trial used certoparin. Two trials used UFH 3 times/day and one trial used UFH twice/day. Overall, compared with UFH, the use of LMWH was associated with a significant reduction in total VTE by 46% (p<0.001), proximal VTE by 47% (p<0.001), and pulmonary embolism by 74% (p=0.042). The rates of bleeding, intracranial hemorrhage, and mortality were not significantly different between the groups. When only the trials that used enoxaparin were considered, the results were consistent with the overall findings. Unfortunately, no sensitivity analysis was conducted evaluating the outcomes based on twice-daily versus thrice-daily dosing of UFH. As patients with ischemic stroke have such a high risk for VTE, this evaluation would have been interesting. Also, this added evaluation would have been beneficial since the only trial that used UFH twice/day was the PREVAIL trial, but it contributed more than 70% of the patients in the meta-analysis.


To our knowledge, this study was the first to evaluate the overall cost to a health care system...
when hospitalized medically ill patients who receive UFH or enoxaparin for the prevention of VTE develop heparin-induced thrombocytopenia (HIT). This retrospective study used nested case-controls from a single hospital. Heparin-induced thrombocytopenia was deemed to have occurred if heparin-dependent antibodies were detected during hospitalization. Each patient with HIT was matched with three control patients without HIT who were identified with prespecified criteria. Hospital and physician charges for the patients with HIT and control subjects were extracted from the hospital's database and compared. All such charges were converted to 2004 dollars to account for inflation.

During the more than 4 years of data collection, 10,121 adult patients received either UFH 5000 U 2 or 3 times/day, or enoxaparin 30 mg twice/day or 40 mg once/day. In patients receiving UFH, the rate of HIT was 0.51%, compared with 0.08% in patients who received enoxaparin (p=0.03). Compared with control patients, the patients who developed HIT incurred an average of $82,266 more in charges. In addition, development of HIT was associated with an extra 12.5 days of hospitalization. Most notably, as a result of the markedly lower rate of HIT in patients receiving enoxaparin compared with those receiving UFH, a total cost savings of $32,981 was observed in patients who received enoxaparin for VTE prophylaxis. This cost savings is equivalent to $13.88/patient, despite the higher acquisition drug cost for enoxaparin. These observations suggest that use of enoxaparin is preferred over UFH for prevention of VTE for both clinical and pharmacoeconomic reasons. It is possible that the savings calculated from this study may actually represent a conservative estimate since the rate of detected HIT was quite a bit lower than the 1–3% typically quoted.

Cancer


Central venous catheters are frequently implanted in patients with malignancy as a means to deliver chemotherapy and other intravenous drugs. These catheters have a tendency to clot, which is typically prevented with local anticoagulation by flushing the catheter with UFH, saline, or other agents. In 1990, a randomized clinical trial comparing warfarin 1 mg/day with no treatment suggested that systemic anticoagulation was valuable in reducing the rate of central venous catheter–related thrombosis. Subsequent trials evaluated systemic anticoagulation with UFH and LMWH and also suggested a role for systemic anticoagulation. However, more recent, well-designed, double-blind, randomized, controlled trials that evaluated warfarin and LMWHs in patients with cancer who have a central venous catheter have not shown any benefit of using systemic anticoagulation to prevent catheter-associated thrombosis. Thus, a meta-analysis was conducted to assess the available literature.

This meta-analysis, one of two published in 2008, combined results from eight randomized controlled trials involving 1428 patients assigned to receive warfarin, UFH, or LMWH, or to placebo or no treatment. One trial compared nadroparin with warfarin 1 mg/day. No statistically significant difference in the rate of catheter-associated thrombosis was observed for warfarin compared with placebo or no treatment (RR 0.75, p=0.63), for UFH or LMWH compared with placebo or no treatment (RR 0.46, p=0.06), or for any systemic anticoagulation (warfarin, UFH, or LMWH) versus placebo or no treatment (RR 0.59, p=0.11). The use of systemic anticoagulation was not associated with any statistically significant increase in the risk of overall bleeding (RR 1.25, p=0.28). The authors concluded that systemic anticoagulation for prevention of central venous catheter thrombosis provides no benefit. An overall decline in the occurrence of catheter-related thrombosis was also noted, likely associated with improvements in catheter design and care, and the routine use of heparin or saline flushes.


The effects of activated coagulation proteases on tumor cell biology and the observation that LMWH may prolong survival in patients with cancer led to speculation that anticoagulation might have benefits beyond the prevention and treatment of thrombosis in patients with cancer. The Fragmin Advanced Malignancy Outcome Study (FAMOUS), a randomized, double-blind, placebo-controlled trial, was designed to
investigate whether routine anticoagulation with an LMWH might improve cancer survival in patients with malignancy but without thrombosis. A total of 385 patients were randomly assigned to receive long-term dalteparin 5000 IU subcutaneously once/day or placebo. The primary goal was to assess mortality after 1 year of therapy, with secondary outcomes that included VTE and bleeding complications. The patients had advanced stage III or IV cancer of the breast, lung, gastrointestinal tract, ovary, or uterus. At 1 year, survival estimates for patients treated with dalteparin and placebo were similar (46% vs 41%, p=0.19). However, a subgroup analysis of 102 patients with a better prognosis and who survived beyond 17 months found a significant survival benefit (p=0.03) for dalteparin at 2 years and at 3 years. The rate of symptomatic VTE was low during the study period (dalteparin 2.4% vs placebo 3.3%), as was the rate of major and minor bleeding (dalteparin 4.7% vs placebo 2.7%). The high early mortality rate in the overall population may have influenced the results. Nevertheless, the trial demonstrated the feasibility, safety, and effectiveness of long-term LMWH in patients with advanced cancer.


After FAMOUS, three additional randomized controlled trials evaluated the mortality benefit of LMWH in patients with malignancy but without thrombosis. Data from all four trials were subsequently combined in this meta-analysis, which compared the effect of LMWH and placebo or no treatment on cancer survival. In total, the studies evaluated 448 patients with solid tumors who were treated with dalteparin 5000 IU subcutaneously once/day or weight-adjusted nadroparin 3600–7200 antifactor Xa U twice/day, for various durations depending on the study involved. An additional 450 patients received placebo or no treatment during the study. With use of OR analysis, the pooled results of the studies showed that LMWH was associated with a 30% reduction in the odds of death at 1 year and a 43% reduction in the odds of death at 2 years. The RR analysis found that LMWH was associated with a 13% reduction in the risk of death at 1 year, and a 10% reduction in the risk of death at 2 years. In contrast to the FAMOUS trial, this meta-analysis found that the survival benefit of LMWH extended to patients with advanced disease. When patients with stage I or II malignancy were excluded, the OR of death at 1 year was 0.75, and the RR of death at 1 year was 0.89. At 2 years, these figures were 0.90 and 0.92, respectively. Despite the results of this meta-analysis, routine use of LMWH in patients with cancer has not become the standard of care. Even primary VTE prophylaxis in patients with cancer is currently not recommended. Future trials will need to determine the effectiveness and cost:benefit ratio of both of these potential strategies.


The Enoxaparin and Cancer (ENOXACAN) trial is a landmark trial that was among the first to establish the effectiveness and safety of an LMWH compared with UFH for the prevention of VTE in patients with malignancy who are undergoing major surgery. The ENOXACAN trial evaluated 631 patients undergoing planned elective curative abdominal or pelvic surgery for cancer who had been randomly assigned to receive either UFH 5000 U subcutaneously 3 times/day or enoxaparin 40 mg subcutaneously once/day. Prophylaxis was started 2 hours before surgery and continued for 10 days in both groups. Bilateral venography was performed in all patients at 10 days or sooner if a patient developed clinical symptoms of VTE. All patients were followed for 3 months. At 10 days, no significant difference was noted in the combined rate of DVT, pulmonary embolism, or death in patients exposed to LMWH or UFH (14.7% vs 18.2%, 95% CI -9.2–2.3, p=NS). The rate of major bleeding was also similar (4.1% vs 2.9%, p=NS). At 3 months, no significant difference in mortality was observed between the two groups. In the subgroup of patients undergoing colorectal surgery and considered to be at higher risk for VTE than the general study population, the rate of VTE was 18.8% in patients treated with UFH and 16.6% in patients treated with enoxaparin. In addition, in the subgroup of patients whose operations lasted longer than 4 hours, the VTE rate was 13.9% in patients treated with UFH and 7.8% in patients treated with enoxaparin. This study was used to support the role of an LMWH in prevention of
cancer-associated thrombosis in patients undergoing surgery.


This systematic review was an evaluation of randomized controlled trials that investigated the role of VTE prophylaxis in patients with cancer who were undergoing surgery. Its aim was to define the overall rate of DVT, the efficacy of high- versus low-dose heparin, and the rate of bleeding complications associated with pharmacologic prophylaxis in this population. Twenty-six trials were included, all of which involved some aspect of pharmacologic VTE prophylaxis, started 2 hours before surgery, in 7639 patients. The overall DVT rate in the control or placebo groups of evaluable studies was 35.2% and was reduced to 12.7% when a heparin product was used for VTE prophylaxis and to 5% when heparin was combined with a mechanical method of VTE prophylaxis. A subgroup analysis found that high-dose LMWH greater than 3400 U/day was associated with a lower rate of DVT than lower dose LMWH (7.9% vs 14.5%, p<0.0001), as was higher dose UFH 5000 U 3 times/day compared with lower dose UFH 5000 U twice/day (8% vs 13.4%, p=0.0132). No significant differences were detected between LMWH and UFH with respect to effectiveness in reducing the rate of DVT compared with placebo or control, or in minor bleeding (10% overall), major bleeding (1% overall), or bleeding requiring discontinuation of pharmacologic prophylaxis (3% overall). This review lends support to the general need for VTE prophylaxis in patients undergoing surgery and reminds readers of regulatory requirements that will drive the need to ensure adequate prophylaxis and to evaluate postoperative VTE rates.


Using a more sophisticated meta-analytic methodology than the systematic review described above, the authors of this study evaluated the combined results of 14 randomized controlled trials that specifically compared an LMWH with UFH in the prevention of VTE in 5822 patients undergoing cancer surgery. The primary objective was to evaluate mortality, which was not significantly different in patients treated with an LMWH compared with those treated with UFH (RR 0.89, 95% CI 0.61–1.28); in addition, no significant differences in mortality rate were observed when LMWH was compared with UFH given twice/day or 3 times/day. A number of subanalyses were conducted, the most significant of which was a comparison of LMWH with different dosing frequencies of UFH. Regardless of the diagnostic strategy used to detect DVT, LMWH was superior to UFH (RR 0.72, 95% CI 0.55–0.84). This benefit was significant in the subgroup receiving UFH twice/day (RR 0.66, 95% CI 0.44–0.99) but not in the subgroup receiving UFH 3 times/day (RR 0.78, 95% CI 0.53–1.15). Of importance, however, no trials directly compared twice-daily with thrice-daily UFH regimens. No significant differences in minor bleeding, major bleeding, hematoma formation, bleeding requiring surgical intervention, or other measures of bleeding were found between groups. This meta-analysis suggests that LMWH is equivalent to UFH given 3 times/day for VTE prophylaxis in patients undergoing cancer surgery, and that any detected difference is driven by comparisons of LMWH with UFH given twice/day, in which LMWH is in fact superior.


The ENOXACAN study published in 1997 compared the efficacy and safety of enoxaparin with that of UFH for VTE prophylaxis in patients undergoing elective cancer surgery and found a significant benefit to using LMWH. Recognizing that the risk of VTE extends beyond the period of hospitalization after major surgery, the ENOXACAN II trial, undertaken by the same study group, aimed to determine the value of extending the duration of VTE prophylaxis. A total of 332 patients requiring open, elective, curative surgery for abdominal or pelvic cancer received enoxaparin 40 mg subcutaneously once/day for 6–10 days as routine VTE prophylaxis. The patients were subsequently randomly assigned to continue either enoxaparin or placebo for an additional 21 days. With use of an intent-to-treat analysis, extended-duration prophylaxis reduced the rate of venographically detected VTE between days 25 and 31 from 12% in the placebo group to 4.8% in the enoxaparin
group (p=0.02). The overall RR was 60%. At 3 months, the difference persisted, with 13.8% in the placebo group and 5.5% in the enoxaparin group (p=0.01). The rate of major bleeding was very low and not significantly different between the two groups.

**Pregnancy**


This article is part of the ACCP Evidence-Based Clinical Practice Guidelines, which were updated in 2008. The article provides informative recommendations with supporting evidence regarding the use of antithrombotic agents, as well as the management of VTE and thrombophilia, during pregnancy. It includes key recommendations for VTE prophylaxis and treatment in pregnancy, mechanical heart valves and thrombophilia in pregnancy, effects of various antithrombotic exposure in utero, fetal complications of antithrombotic therapy, use of antithrombotics in nursing women, and implications of women's preferences and values during pregnancy. These updated guidelines include strong evidence for substituting warfarin with UFH or LMWH in pregnant women and screening for antiphospholipid antibodies, as well as contemporary recommendations for pregnant women with thrombophilia, including the practice of VTE prophylaxis in the ante- and postpartum periods. New sections include direct thrombin inhibitor and pentasaccharide use in utero, thrombolysis use during pregnancy, and VTE after cesarean section.


Hereditary thrombophilias have been associated with fetal loss and are often the cause of recurrent miscarriages. This case-control study of 85 patients examines whether the use of enoxaparin 40 mg subcutaneously once/day is effective at increasing live birth rates among women with a history of recurrent miscarriages and a hereditary thrombophilia. Women were included in the study if they had three or more previous and consecutive pregnancy losses in the first or second trimester. Results showed that patients treated with enoxaparin throughout pregnancy had a significantly higher live birth rate compared with controls (70.2% vs 43.8%, p=0.02). This beneficial effect was apparent primarily among those women with a history of no previous live births (p=0.008), in whom enoxaparin resulted in a 10-fold increase in the OR for a live birth.

This study also analyzed the proportion of live births for different types of documented hereditary thrombophilia. Enoxaparin was found to increase live birth rates in each of the thrombophilias tested, except for those women with the prothrombin gene mutation. The greatest beneficial effect was seen in those women with factor V Leiden. Although larger studies are required before thromboprophylaxis with enoxaparin becomes the standard of practice in this patient population, this study provides data that enoxaparin may have a role in preventing further pregnancy losses in women with a history of recurrent miscarriages and hereditary thrombophilia.


Women are in a hypercoagulable state and at increased risk for thrombosis during pregnancy. When additional risk factors (such as previous idiopathic VTE, thrombophilia, or both) are present, the thrombosis risk is further increased, most significantly within the first trimester. The most optimal VTE prevention strategy in this patient population is unknown. This large, prospective study evaluated a risk assessment strategy and prophylaxis regimen for those pregnant women at increased VTE risk because of a history of VTE and thrombophilia. The study assigned 810 pregnant women to one of three risk groups according to individual risk at the time of presentation. The most common risk factors were thrombophilias (~75%), history of previous VTE (~60%), and family history of VTE (~31%). All patients received daily doses of subcutaneous dalteparin, although the frequency, dose, and length of prophylaxis varied among risk groups.

The results demonstrated that this particular risk stratification and prophylaxis strategy in pregnant women at increased risk for VTE resulted in low levels of symptomatic VTE events. Objectively confirmed VTE by ultrasonography,
Obese patients undergoing bariatric surgery warrant VTE prophylaxis because they are at high risk for developing a fatal pulmonary embolism or postthrombotic syndrome. However, a consensus does not exist on the most effective prophylactic approach, including agent selection, dosage, and schedule. It is difficult to extrapolate data from other comparative trials given that the inclusion of this patient population is limited. This prospective, randomized, pilot trial evaluated the safety and efficacy of a lower fixed dose compared with a higher fixed dose of nadroparin for the prophylaxis of postoperative thromboembolism in patients undergoing gastric bypass surgery for morbid obesity (body mass index [BMI] > 36 kg/m²). According to a parallel study design, 30 patients received subcutaneous nadroparin 0.6 ml/day (5700 antifactor Xa U), and another 30 patients received subcutaneous nadroparin 1.0 ml/day (9500 antifactor Xa U). Both doses were started 1 day before surgery. The primary end point of rate of VTE was evaluated by using compression ultrasonography, and results showed no thrombotic events in any patients after surgery, at discharge, or at the 3- and 6-month follow-up periods in either group. No bleeding events were reported in the lower dose group, but in the higher dose group two patients developed major hemorrhages. The study provides evidence that the once-daily administration of a lower fixed dose of nadroparin was as effective as the higher dose in preventing VTE and was safer, because of fewer bleeding events, in this morbidly obese population. This pilot, single-center study provides the rationale for developing a larger, randomized study within this patient population, to indicate that a single daily dose of nadroparin, unadjusted for BMI, may be sufficient for VTE prophylaxis in those patients undergoing bariatric surgery.


Patients undergoing bariatric surgery are at high risk for VTE. Morbid obesity is an independent risk factor for sudden death from acute pulmonary embolism. The LMWHs have been increasingly used for VTE prophylaxis, but their efficacy in morbidly obese patients is unknown. This study explored LMWH use in morbidly obese patients undergoing either primary or revisional bariatric surgery at an
active bariatric surgical practice. The study used a multimodal approach for VTE prophylaxis in 481 patients based on the recommendation for highest-risk patients as assessed by a thrombosis risk assessment tool. Patients were to receive a combination of early ambulation, GCS, IPC, and twice-daily administration of enoxaparin beginning 2 hours before surgery and continued until the patients were fully ambulatory or until discharge, whichever came first. Patients received enoxaparin either 30 or 40 mg every 12 hours. Primary bariatric surgery was performed in most of the patients (91.5%), whose average BMI was approximately 51 kg/m². Patients who received the higher dose of enoxaparin had decreased VTE events compared with those receiving the lower enoxaparin dose (two DVTs vs one DVT and four nonfatal pulmonary embolisms, p<0.01). There was one bleeding complication in each group, neither of which was life-threatening. This study provides data that in morbidly obese patients undergoing bariatric surgery, enoxaparin 40 mg twice/day may be more effective in preventing VTE than the lower dose regimen.


This study sought to correlate antifactor Xa activity with body weight after an injection of enoxaparin. An LMWH is a first-line choice for VTE prophylaxis for various surgical procedures, but the efficacy of LMWH in preventing clinically significant VTE events has not been studied adequately in obese patients. Such a study is unlikely to be performed given the large number of patients that would be necessary to detect a difference due to the low frequency of events. However, the effect of a given enoxaparin dose can be monitored through plasma antifactor Xa levels. This study recruited 17 patients undergoing surgical procedures, 10 of whom were undergoing bariatric surgery. Antifactor Xa levels were drawn hourly for 6 hours, then every 2 hours for two more levels, after an enoxaparin 40-mg subcutaneous dose was given 20 hours before surgery. The study found no resultant VTE events and no excessive bleeding in any of the patients. Peak levels of antifactor Xa were found to occur 3–5 hours after enoxaparin was administered. Further studies will be needed to address the safety of adjusting LMWH dosages to achieve similar antifactor Xa activity among patients of various weights.


Morbidly obese patients undergoing bariatric surgery are at high risk for VTE. However, numerous factors complicate the selection of VTE prophylaxis in this population, including decreased venous return from pneumoperitoneum, poor effectiveness of GCS, and unclear pharmacodynamics of heparin administration. Researchers in this study used a protocol of continuous, non-weight-based, intravenous UFH infusion, starting 1 hour before surgery, for VTE prophylaxis. The UFH infusions were started at 400 U/hour and continued until the day of discharge. No UFH bolus was given, nor were dosage adjustments made based on weight, activated partial thromboplastin time, or antifactor Xa levels. In addition, IPCs were used, and ambulation was strongly encouraged. No routine surveillance studies were performed; however, all clinically evident VTE events were recorded. Results showed that only 1 (0.12%) of 822 patients receiving the UFH infusion developed a pulmonary embolism after the gastric bypass procedure, and UFH therapy was temporarily held or stopped in 5% of patients because of postoperative bleeding. The authors concluded that a continuous low-dose intravenous UFH infusion is associated with a low rate of VTE events and hemorrhage and, therefore, is a potential option for VTE prophylaxis in this patient population.


The goal of the Prophylaxis Against VTE Outcomes in Bariatric Surgery Patients Receiving Enoxaparin (PROBE) study was to retrospectively gather information on symptomatic VTE and bleeding events in patients who underwent bariatric surgery and were given various regimens of enoxaparin for VTE prophylaxis in five study centers throughout the United States. The study
included 668 patients with an average preoperative BMI of 49.6 kg/m², most of whom (84.9%) underwent open gastric bypass surgery with mean postoperative follow-up of 10.5 days. Each center used a different enoxaparin dosing regimen for prophylaxis, including enoxaparin 30 mg started preoperatively, 30 mg/day started after hospital discharge, 40 mg/day started postoperatively, and 40 mg twice/day started postoperatively. The duration of prophylaxis also varied, ranging from 12 hours to 10 days.

Cumulatively, 1.0% of patients had VTE events after surgery (0.1% DVT and 0.9% pulmonary embolism), all of which occurred after the cessation of prophylaxis. The highest rates of VTE were found in those patients who received enoxaparin 30 mg/day beginning after discharge. Among those patients who received enoxaparin perioperatively, no DVTs were reported and 0.7% had a pulmonary embolism. All patients who experienced a VTE had one or more additional risk factors for VTE aside from severe obesity and abdominal surgery, the most frequent being advanced age and smoking. Few bleeding complications occurred. The six reported nonfatal bleeding events were observed in those centers that administered 40 mg/day or 40 mg twice/day.

This study confirms that morbidly obese patients undergoing bariatric surgery are at substantial risk for VTE complications, despite receiving prophylaxis. Although minimal data from randomized controlled trials exist regarding the optimal enoxaparin regimen for prophylaxis in this population, the data from this study indicate the necessity for additional risk profiling for such patients, describe regimens that may be superior to others, and suggest that extended prophylaxis may be warranted.


The original PREVENT trial found that a fixed dose of dalteparin was effective in reducing VTE events by 45% (RR 0.55, 95% CI 0.38–0.80) in patients aged 40 years or older who require hospitalization for an acute medical illness. This subgroup analysis of the PREVENT trial was conducted to determine whether this fixed dose was as effective in obese patients as in nonobese patients. The authors retrospectively analyzed data from 3706 hospitalized patients included in the PREVENT trial who received dalteparin 5000 IU/day or placebo. Obesity was defined as a BMI greater than 30 kg/m² for men and 28.6 kg/m² for women, and 30.4% of the overall population met these criteria.

In obese patients, the primary end point—a composite of symptomatic VTE, fatal pulmonary embolism, sudden death, or asymptomatic proximal DVT by day 21—occurred in 2.8% of the dalteparin group compared with 4.3% in the placebo group (RR 0.64, 95% CI 0.32–1.28). In nonobese patients, the primary end point occurred in 2.8% of the dalteparin group and 5.2% of the placebo group (RR 0.53, 95% CI 0.34–0.82). Dalteparin was therefore effective in obese patients, with an RRR of 36% across BMI subgroups, except for those patients with a BMI greater than 40 kg/m². This indicates that perhaps a fixed low dose of dalteparin may not be appropriate in the morbidly obese population, particularly in those with additional risk factors. Dalteparin was deemed safe in the obese population, in that no increase in mortality (4.6% vs 2.7%, p=0.14) or increase in major hemorrhage (0% vs 0.7%, p=0.99) versus placebo, was observed by day 21. This study's findings imply a low fixed dose of dalteparin is safe and effective in preventing VTE among hospitalized patients with acute medical illness and is not significantly affected by BMI, unless patients have a BMI greater than 40 kg/m².


The risk of postoperative bleeding must be weighed against the risk of postoperative VTE events in those patients undergoing laparoscopic gastric bypass surgery. This study prospectively evaluated 30-day VTE and bleeding events in 476 patients, half of whom received enoxaparin and the other half received UFH for VTE prophylaxis. The enoxaparin regimen consisted of 40 mg subcutaneously before surgery, then 40 mg on the evening of postoperative day 0 and twice/day until discharge. The UFH regimen consisted of 5000 U subcutaneously before surgery, nothing on the evening of postoperative day 0, and 5000 U 3 times/day until discharge. All patients were also treated with IPC and early ambulation.

No DVT events occurred in either cohort.
(p=0.999), and one pulmonary embolism occurred in the UFH group (p=0.999). Postoperative transfusions were required in 5.9% of the enoxaparin group, compared with 1.3% in the UFH group (p=0.011). In addition, 1.7% of patients in the enoxaparin group required reexploration for bleeding, compared with none in the UFH group (p=0.123). Both regimens were effective in preventing VTE; however, this study suggests UFH as the preferred option for VTE prophylaxis in this patient population because of decreased bleeding complications.

Renal Insufficiency and Dialysis


In this open-label, multicenter, parallel-group study, the impact of renal function on the pharmacokinetic and pharmacodynamic profile of enoxaparin 40 mg once/day was evaluated in cohorts of 12 patients each who had normal, mild, moderate, or severe renal impairment. Both antifactor Xa and antifactor IIa activity were measured over 24–36 hours on days 1 and 4 by using chromogenic assays. A small and gradual increase in the measured 3-hour postdose peak antifactor Xa activity after the fourth dose was observed as renal function declined. At 24 hours, no significant difference in antifactor Xa activity was apparent among the degrees of renal insufficiency, with the exception of those with severe renal impairment (creatinine clearance < 30 ml/min), who had a 39% lower clearance by antifactor Xa compared with the healthy controls (p=0.0001). No clear association was noted between the antifactor Xa activity level and observed bleeding with the prophylactic dose. Although no conclusion was made about mild-to-moderate renal insufficiency, the results supported a potential need to reduce the dosage of enoxaparin in patients with severe renal impairment. The impact of severe renal impairment requiring hemodialysis on enoxaparin was not addressed.


The pharmacokinetics of enoxaparin 40 mg (28 patients) and that of tinzaparin 4500 antifactor Xa U (27 patients) were explored in this prospective, open-label, randomized, two-hospital, parallel-design analysis of a consecutive series of patients older than 75 years with concurrent renal impairment, defined as a estimated creatinine clearance of 20–50 ml/minute. Despite a higher antifactor Xa activity dose of tinzaparin, it still yielded lower mean antifactor Xa activity at days 1 and 8 of 0.44 and 0.46 U/ml (p=0.296) compared with 0.55 and 0.67 U/ml for enoxaparin (p<0.001). Independently, each agent did not show a significant correlation between estimated creatinine clearance and measured antifactor Xa activity. However, it should be noted that the sample was small. This suggests that the presence of renal insufficiency may prolong the clearance of enoxaparin to a greater extent than tinzaparin, and that each agent should be considered independently when determining whether to reduce the dosage as renal function declines.


In this meta-analysis, antifactor Xa levels and the frequency of bleeding in patients with a creatinine clearance of either 30 ml/minute or less, or greater than 30 ml/minute were compared for treatment or prophylactic dosing of tinzaparin, dalteparin, or enoxaparin. Direct observations or subgroups from randomized trials that included patients with renal insufficiency (excluding those requiring hemodialysis) who had received an LMWH were included. Either the Modification of Diet in Renal Disease or Cockcroft-Gault equation was used to quantify renal function, creating a potential bias in the meta-analysis. Eighteen studies met the inclusion criteria. The measured peak antifactor Xa level at 4 hours was significantly higher if the creatinine clearance was below 30 ml/minute, a finding most influenced by enoxaparin compared with tinzaparin or dalteparin. The use of LMWH was associated with an increase in the risk for major bleeding in patients with creatinine clearance less than 30 ml/minute compared to those with a creatinine clearance greater than 30 ml/minute (5.0% vs 2.4%, OR 2.25, 95% CI 1.19–4.27, p=0.013). Major bleeding was also increased when a standard therapeutic dose of enoxaparin
was used (8.3% vs 2.4%, OR 3.88, 95% CI 1.78–8.45) but was not increased when an empirically adjusted dosage of enoxaparin was used (0.9% vs 1.9%, OR 0.58, 95% CI 0.09–3.78, p=0.23 for heterogeneity). Not enough data were available to determine whether adjustments in the dosages of dalteparin or tinzaparin might reduce the risk of bleeding in patients with renal impairment.


Clinical trials frequently exclude patients with renal failure who require hemodialysis, yet these patients have an increased risk for bleeding when exposed to heparins. These patients may require local anticoagulation to maintain the patency of the dialysis circuit or systemic anticoagulation for treatment or prevention of venous or arterial thrombosis. In this meta-analysis, the characteristics of LMWH administered for prevention of extracorporeal thrombosis in patients with end-stage renal disease requiring long-term hemodialysis were explored. Randomized trials published between 1966 and 2004 that used the LMWHs dalteparin (eight trials), nadroparin (five), tinzaparin (three), and enoxaparin (two) during hemodialysis were identified and compared with respect to bleeding rates and the development of dialysis-circuit thrombosis. Dosing in antifactor Xa U varied, but was mostly in the established range for prophylaxis. Note that ideal targets for antifactor Xa activity in this population have not been established.

Most bleeding was considered minor, primarily occurring at vascular access sites. In the 11 trials that compared an LMWH with UFH, no significant difference in the combined major and minor bleeding rate was observed, with an RRR of 0.96 favoring UFH (95% CI 0.27–3.43, p=0.95). Prevention of thrombosis of the extracorporeal circuit favored UFH, but it was not significant, with an RR of 1.15 (95% CI 0.7–1.91). However, the UFH and LMWH doses administered were not consistent among the trials. The characteristics of LMWH in the setting of acute renal failure and associated approaches to renal replacement were not explored. There remains very little literature about the use of LMWHs in patients who require dialysis; therefore, this meta-analysis is an important consideration for clinicians.

**Long-Distance Travel**


The true risk of VTE in patients traveling on flights longer than 6 hours in duration is unknown. These investigators attempted to define the risk of VTE in low-risk patients and establish the effectiveness of GCS for VTE prevention. Travelers at low risk for VTE and seated in economy class for a flight lasting more than 8 hours were randomly assigned to no mechanical prophylaxis or below-knee GCS (20–30 mm Hg). Travelers were advised to place the stockings on before boarding and to remove them immediately on arrival. Low-risk volunteers were enrolled by excluding those with previous VTE, cardiorespiratory disease, and malignancy. The presence of VTE by duplex ultrasonography was the primary end point. Secondary end points were described as superficial thrombophlebitis and D-dimer elevation.

Twelve (10%) of 116 passengers not wearing GCS developed an asymptomatic DVT in the calf. None of the 115 passengers wearing GCS developed a VTE. Thrombophlebitis was detected in none of the control patients and in 3% of people wearing GCS. No relationship in D-dimer was observed, possibly due to the short half-life of D-dimer and the lag time from arrival to drawing blood. These data established the degree of risk associated with VTE in low-risk patients (~1 in 10). In addition, GCS were associated with a reduction in asymptomatic VTE in flights lasting longer than 8 hours.


The Prevention of Venous Thrombosis in Long-Haul Flights (LONFLIT) trials have studied various questions regarding VTE prevention in the setting of extended travel times. The LONFLIT-3 trial evaluated the effectiveness of two pharmacologic methods for VTE prevention compared with a control group. Travelers were deemed high risk by including those with a previous VTE, coagulation disorders, severe obesity, malignancy, and large varicose veins.
Participants were randomly assigned to receive placebo, aspirin 400 mg/day for 3 days starting 12 hours before departure, or one dose of subcutaneous enoxaparin 1 mg/kg given 2–4 hours before departure. All passengers were educated on additional preventive measures such as hydration, in-flight exercises, and avoidance of restrictive baggage and clothes. The primary outcome was the occurrence of DVT and superficial thrombosis confirmed by duplex ultrasonography. Thromboses were detected in 4.8%, 3.6%, and 0.6% (p<0.002) of passengers assigned to placebo, aspirin, and enoxaparin, respectively. In addition, 85% of thrombotic events occurred in passengers ticketed in nonaisle seats. No adverse effects were noted with enoxaparin; however, 13% of the patients experienced gastrointestinal symptoms. This trial underscores the need for prophylaxis in high-risk patients traveling on long flights, the relative ineffectiveness of aspirin for VTE prevention, and potential need for preferred seating for those at risk for thrombosis. These data also demonstrate the benefits of pharmacologic prophylaxis when used in combination with other strategies such as hydration and in-flight exercises.


The LONFLIT-5 study evaluated the effectiveness of GCS in high-risk patients traveling on flights lasting from 11–13 hours. Travelers were deemed high risk if they had a previous VTE, coagulation disorders, severe obesity, malignancy, and large varicose veins. Participants were randomly assigned to control or below-knee GCS (14–17 mm Hg). Subjects were advised to wear the GCS 3–4 hours before their flight and to remove them after deplaning. All travelers were educated on a mild exercise regimen, avoidance of restrictive seating, and hydration. The primary outcome was defined as VTE by ultrasonographic scanning. D-dimer and fibrinogen serum levels were measured before departure (within 12 hrs) and after arrival (within 4 hrs). Among the patients assigned to GCS, one developed a distal DVT (0.97%), whereas six patients (5.8%, p<0.0025) in the control group developed a DVT. Among women who experienced an event, all had been taking low-dose oral contraceptive therapy for at least 12 months. D-dimer and fibrinogen levels were significantly different between subjects with thrombosis and those without thrombosis. These data demonstrate the effectiveness of GCS in high-risk travelers for the prevention of asymptomatic DVT. In addition, the high rate of DVT in the control group illustrates the need for increased awareness of VTE on very long flights.


This Cochrane review assesses the effectiveness of GCS in passengers on flights lasting at least 4 hours. Ten randomized trials, representing a total of 2856 people, were included in this analysis. Nine of the trials examined the effectiveness of bilateral GCS, and one trial investigated unilateral GCS. Eight of the 10 trials included experiences from the LONFLIT studies. The primary outcome was the diagnosis of symptomatic or asymptomatic DVT by ultrasonography or venography. Secondary analyses included the diagnosis of pulmonary embolism, death, superficial vein thrombosis, and adverse effects. A total of 50 people developed asymptomatic DVT (three in the GCS groups and 47 in the placebo group). None of the participants experienced symptomatic DVT, pulmonary embolism, or adverse effects. A total of 16 people developed superficial vein thrombosis (four in the GCS groups and 12 in the placebo group). This review confirms that use of GCS reduces asymptomatic DVT from approximately 10/1000 to 2 or 3/1000. A thorough review of potential pathophysiologic mechanisms responsible for the development of thromboses during air travel is included.


Although many tertiary resources are available for VTE prevention during long flights, most of these analyses focus on a single prophylactic strategy. These investigators included 25 trials that reported primary outcomes for various preventive VTE measures during long-distance travel. Four variables were significantly predictive of VTE: method of screening (ultrasonography, OR 390%, p<0.0001), type of primary outcome (DVT only, OR 23%; all VTE,
OR 21%, p<0.0001), clinical risk of thrombosis (high risk, OR 3.6%, p<0.0001), and duration of long distance travel (> 8 hrs, OR 2.3%, p<0.0001). Overall, asymptomatic VTE was more common than symptomatic DVT and pulmonary embolism. Graduated compression stockings and LMWH prevented VTE associated with long-distance travel, whereas aspirin provided no clinical benefit. The authors recommend hydration and frequent in-flight exercises for all patients. Travelers with low thrombotic risk on a flight lasting less than 6 hours require no prophylaxis. Those passengers with at least one risk factor for thrombosis or flying longer than 6 hours should consider GCS or LMWH. The article serves as an excellent resource with a very thorough summary (detailed table spanning three pages) of all the major trials investigating long-flight VTE prophylaxis.

Mechanical Prophylaxis


Sequential compression devices (SCDs) have become an alternative in the prevention of VTE. Their popularity has grown in patients with contraindications to UFH; however, anecdotal evidence has suggested that compliance with these devices is poor. The investigators evaluated compliance with SCDs in nonambulatory trauma patients. Six observations were made during a 24-hour period to assess the presence and functioning of SCDs in 227 patients. Full compliance was defined as SCDs that were on and functioning at all six observations. Only 42 patients (19%) were classified as fully compliant. Of the 1343 available observations, SCDs were on and functioning in only 712 observations (53%). The most common periods of noncompliance were the mid-morning and early afternoon. In those patients reported as noncompliant, one thrombotic risk factor was present in 83% and multiple risk factors in 41%. Some clinicians view SCDs as a prophylactic option relatively easy to use and order. This trial demonstrates the need for continued education and may highlight key hospital shifts to initially target. The effectiveness of SCDs has been reported; however, these findings have occurred in the well-controlled environment of a clinical trial.


Current guidelines suggest IPC as an option for VTE prophylaxis in patients undergoing gynecologic surgery. The investigators conducted a retrospective review to identify patients who failed IPC. In those patients who experienced an event, an association between VTE risk factors and the occurrence of VTE was measured. The overall frequency of VTE in 1862 patients undergoing gynecologic surgery was 1.3%. These events consisted of 9 DVTs and 15 pulmonary embolisms. After multivariable regression analysis, three independent prognostic factors were identified: cancer (OR 3.8, p=0.001), history of DVT (OR 5.3, p=0.006), and age older than 60 years (OR 2.6, p=0.04). Patients with two or three of these significant risk factors had a 3.2% rate of VTE compared with 0.6% in patients with zero or one risk factor. These data afford clinicians the ability to screen or stratify patients undergoing gynecologic surgery by VTE risk. Clinicians treating women with more than one risk factor should consider pharmacologic rather than mechanical strategies to prevent VTE.


The management of DVT often includes the goal of pulmonary embolism prevention. However, postthrombotic syndrome occurs in nearly 30% of patients with a proximal DVT and is often underrecognized. These investigators evaluated the efficacy of GCS for the prevention of postthrombotic syndrome over 2 years. Patients who had developed VTE were randomly assigned to no stockings or GCS with 30–40 mm Hg pressure. Patients also received standard pharmacologic therapy for 3–6 months. A standardized scale was used to evaluate the presence and severity of postthrombotic syndrome. Postthrombotic syndrome was present in 44 (49%) of 90 patients assigned to no stockings compared with 23 (26%) of 90 patients using GCS. Of those control patients who developed postthrombotic syndrome, 10 cases were considered severe compared with three cases in the patients using GCS. Most diagnoses of postthrombotic syndrome (40% in the control group and 21% in the GCS group) were made in the first 6 months, with most patients receiving
oral anticoagulation. Two independent risk factors for the development of postthrombotic syndrome were identified: ipsilateral DVT (HR 3.32, p=0.04) and 10-year increments of age (HR 1.36, p=0.003). This landmark trial confirms the high rate of postthrombotic syndrome (50%), demonstrates the effectiveness of GCS in combination with anticoagulation (approximately 50% reduction), and identifies factors associated with development of postthrombotic syndrome.


Long-term safety and efficacy data on vena cava filters have been scarce and unreliable. The Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (PREPIC) trial, the largest vena cava filter trial to our knowledge, reported a reduction in pulmonary embolism at the 2-year follow-up. However, this benefit was overshadowed by an increase in DVT and no mortality benefit. The PREPIC 8-year follow-up was performed to assess the long-term safety and efficacy of permanent vena cava filter insertion. Patients with a diagnosis of acute proximal DVT and considered high risk for the development of pulmonary embolism were enrolled. Pulmonary embolism occurred in 9 patients with a filter (6.2%) and 24 patients without a filter (15.1%, p=0.008). Deep vein thrombosis was discovered in 57 patients with a filter (35.7%) and 41 patients without a filter (25.7%, p=0.042). No significant difference in rates of postthrombotic syndrome and mortality were observed. Of interest, 24 patients without a filter (46%) developed a pulmonary embolism despite receiving vitamin K antagonist therapy. Several key patient demographics and GCS variables were underrepresented in this review, and care should be taken when extrapolating the results. In addition to the fact that no low-risk patients were included in this review, the effect of GCS duration, length, and pressure were not assessed. Also, the GCS were compared with control rather than anticoagulation, limiting the results of the analysis.


Although pharmacologic VTE prophylaxis is the preferred strategy in moderate- or high-risk patients undergoing surgery, many of these patients have contraindications to anticoagulation. Investigators performed a meta-analysis to evaluate the effectiveness of IPC in patients who had surgery. A total of 2270 patients from 15 trials (surgeries included general, orthopedic, neurosurgery, oncologic, and urologic) were eligible for inclusion. Initiation of IPC varied in trials and was classified as preoperative (before anesthesia), perioperative (immediately after anesthesia), and postoperative (< 24 hrs after surgery). The RRR of DVT was 60% (RR 0.40, 95% CI 0.29–0.56, p<0.001) in patients wearing IPC compared with no IPC. The use of IPC did not reduce pulmonary embolism compared with the control group (p=0.7). In addition, the
occurrence of DVT did not differ significantly between patients for whom IPC was started before surgery and those for whom IPC was started after surgery. These data ensure clinicians that patients undergoing surgery do benefit from initiation of IPC for VTE prophylaxis. This review also demonstrates that the timing of IPC initiation around surgery is not clinically important.


Although uncommon, DVT and pulmonary embolism are clinically important complications of stroke. Anticoagulants reduce the risk of VTE; however, this benefit is offset by the risk of hemorrhage. This Cochrane review was conducted to assess the effectiveness of mechanical prophylaxis for VTE prevention in patients with stroke. Despite the large number of studies considered for this analysis, the stringent inclusion criteria allowed only two studies (123 patients) to be included. Overall, mechanical prophylaxis methods were not associated with a decreased rate of DVT in survivors (OR 0.54, 95% CI 0.18–1.57) or in those who died (OR 1.54, 95% CI 0.5–4.77). This review demonstrates the disparity of data in this high-risk group of patients. Although no firm conclusions can be drawn from this analysis regarding the efficacy of mechanical prophylaxis, the strategy appears safe in patients with stroke.

Extended Prophylaxis


This trial is discussed in the Orthopedic Surgery section; however, a discussion in this section is also warranted. This meta-analysis of nine studies involving 3999 patients helped establish the current ACCP recommendations to consider extending prophylaxis beyond 10 days and up to 35 days after THR and TKR surgeries. Although all individual studies included in the analysis had shown a reduction in symptomatic VTE after 4–6 weeks of extended prophylaxis compared with in-hospital prophylaxis, statistical significance was reached in only two of nine studies. The combined results showed a significant decrease in symptomatic VTE (3.3% vs 1.3%, OR 0.38). Similar RR was demonstrated for proximal DVT (9.1% vs 2.9%, OR 0.33) and symptomatic pulmonary embolism (0.6% vs 0.2%, OR 0.43), but the pulmonary embolism end point did not reach significance secondary to the relatively low event rate. Major bleeding was rare (0.2%) overall in the out-of-hospital period and did not differ significantly between groups, but there was a small but significant increase in minor bleeding (3.7% vs 2.5%) in the extended prophylaxis group. Results did not vary according to the duration of in-hospital prophylaxis (4–15 days) or whether or not mandatory venography was required in the individual trial before hospital discharge.

An important prespecified subgroup analysis showed that the reduction in symptomatic events was greater for extended prophylaxis versus in-hospital prophylaxis in patients undergoing THR (1.3% vs 4.3%, OR 0.33) compared with those undergoing TKR (1.0% vs 1.4%, OR 0.74). It should be noted that only two studies examined both TKR and THR, whereas seven examined THR exclusively. However, the findings are consistent with those of previous studies, which demonstrated that a greater percentage of VTE after TKR are asymptomatic and that the time course of symptomatic events with TKR occurs earlier than with THR. Hence, the ACCP recommendations for extended prophylaxis with THR (grade 1A) are stronger than those for TKR (grade 2B).


This review included six of the nine studies included in the meta-analysis above but provided a more focused examination, since it was limited to elective THR. The LMWHs were the sole extended prophylaxis option, and all trials used placebo as the comparator. Bilateral ascending venography was the only diagnostic test allowed for identifying DVT in these studies. The studies were all double-blind and involved more than 1950 patients receiving once-daily enoxaparin (three studies) or once-daily dalteparin (three studies) for 18–29 days after hospitalization. Combined results showed significant reductions in favor of extended LMWH prophylaxis for all DVT (22.5% vs 7.9%, RR 0.41), proximal DVT
KEY ARTICLES FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM  
Dobesh et al

(11.2% vs 3.0%, RR 0.31), and symptomatic DVT (4.2% vs 1.4%, RR 0.36). Unlike the previous meta-analysis, these benefits were realized without a significant difference in minor bleeding (2.66% with LMWH vs 2.44% with placebo). Major bleeding again was rare, with report of only one case in the placebo group and none in the LMWH group during the out-of-hospital period. The review provides valuable information from the individual trials such as the number of patients with previous VTE or cancer and the proportion undergoing successful venography. The length of inpatient prophylaxis did not impact the subsequent results.

The relatively low 15 patients needed to treat to prevent one proximal DVT or 45 to prevent one symptomatic VTE with minimal bleeding risk in the posthospital period in this review provide the basis for the consideration of extended prophylaxis for THR, and serves as a benchmark of comparison for extended prophylaxis in other clinical scenarios. Most cost-effectiveness evaluations have concluded that extended prophylaxis for THR is cost saving or a worthwhile expense given the events prevented. Oral vitamin K antagonists have since demonstrated efficacy with extended prophylaxis in THR, but their benefit in clinical trials has been offset by a higher risk of bleeding than with LMWH.


The Pentasaccharide in Hip-Fracture Surgery (PENTHIFIRA) Plus trial was a multicenter trial that examined 656 patients receiving 6–8 days of fondaparinux 2.5 mg/day after undergoing hip fracture surgery and followed up by randomization in a double-blind fashion to receive placebo or continued fondaparinux for 19–23 days. Bilateral venography was performed at 25–32 days. This population was selected after past studies had shown a higher rate of fatal pulmonary embolism in patients undergoing hip fracture surgery than in those undergoing THR and a majority of symptomatic events occurring beyond day 11 after surgery. Significant reductions were seen with extended fondaparinux for all VTE (35.0% vs 1.4%) and proximal DVT (15.8 vs 0.9%). For symptomatic VTE, the reduction was significant (2.7% vs 0.3%) but with much fewer events. Symptomatic pulmonary embolism was observed in three patients, all receiving placebo, with one being fatal. Major bleeding (2.4% vs 0.6%, p=0.06), minor bleeding (1.5% vs 0.6%), and need for transfusions (8.9% vs 6.1%) were all insignificantly higher with fondaparinux than placebo. Probably owing to the advanced age and underlying frailty of the patient population, the mean length of hospitalization during this study was 13.5 days. A lower percentage of patients than seen in THR studies, 65%, had adequate venography to evaluate DVT. This study demonstrates a very impressive RRR of approximately 90% for fondaparinux in hip fracture surgery for all efficacy end points. The absolute RR of 2.4% for symptomatic VTE is similar to that seen for LMWH extended prophylaxis in THR. As a result of this trial, the ACCP recommends that VTE prophylaxis be extended beyond 10 days and up to 35 days for hip fracture surgery (grade 1A), and fondaparinux carries the only grade 1A for extended prophylaxis in patients undergoing hip fracture surgery.


This trial is discussed in the Cancer section, but a discussion here is also warranted. In one of the first major trials to examine extended prophylaxis outside of orthopedic surgery, ENOXACAN II, 332 patients having undergone planned curative surgery for abdominal or pelvic cancer and subsequent prophylaxis with 6–10 days of open-label enoxaparin 40 mg/day were randomly assigned to either continuation of enoxaparin 40 mg or placebo daily for 21 more days. Over 80% of the surgeries were performed on the gastrointestinal tract, whereas approximately 8% involved female reproductive organs. Bilateral venography was then performed at 25–31 days. Patients were followed 3 months, in part to see if extended prophylaxis merely delayed, rather than prevented, the onset of VTE. A significant reduction in the primary end point of all VTE was seen with enoxaparin (12.0% vs 4.8%, RR 60%, p=0.02) compared with placebo. However, of the 28 events reported during the 21-day double-blind period, 27 of them were asymptomatic and 24 were distal vein DVTs. Only one pulmonary embolism was detected.
during that time frame. Therefore, with these relatively low event rates, the absolute RRs for proximal DVT (1.8% vs 0.6%, absolute RR 1.2%, number needed to treat 83) and symptomatic VTE (0.6% vs 0%, number needed to treat 167) were not significant. Bleeding events during the 21-day double-blind period were not significantly different between enoxaparin and placebo (major bleeding 0.4% vs 0% and minor bleeding 4.7% vs 3.6%). During the period between venography and the end of the 3-month follow-up, three of the four symptomatic VTE events that occurred were from the group that had received placebo. This demonstrated that extended prophylaxis helped to prevent VTE formation and did not merely delay its onset.


This article details the methodology of the Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) trial, which was designed after results of previous studies in medically ill patients demonstrated that an increased risk of VTE may continue for an extended duration and suggested a potential mortality benefit if an adequately powered trial were performed. The EXCLAIM trial enrolled more than 5100 hospitalized patients in 264 centers in 18 countries who had recent reduced mobility and at least one other risk factor for VTE. All patients received open-label enoxaparin 40 mg/day for a mean ± SD of 10 ± 4 days before being randomly assigned to double-blind therapy with either continued enoxaparin 40 mg or placebo daily for an additional 28 ± 4 days. At the end of the double-blind treatment period, all patients underwent bilateral compression ultrasonographic testing, which was different from most trials in which bilateral venography was used. Patients were then followed for an additional mean ± SD of 142 ± 10 days for symptomatic events.

Some of the results of the trial have been announced but have not been formally published as of the time of this writing. A planned, blinded, interim analysis allowed the steering committee to redefine some inclusion criteria to allow enrollment of patients with a higher risk for VTE (recent immobility plus age > 75 yrs, history of VTE, or previous diagnosis of cancer). How this affected who constituted the final study population awaits further examination. This is especially important in light of the announced results (presented at the International Society of Hematology meeting in 2007) that demonstrated an impressive, significant 44% RRR in all VTE (4.9% vs 2.8%) and 73% in symptomatic VTE (1.1% vs 0.3%) in favor of prolonged LMWH prophylaxis. It may be argued that ultrasonographic examination is more reflective of current practice, but that greater absolute reductions may have been realized by using a more sensitive test such as venography. However, unlike most other trials of extended prophylaxis, significantly more major (0.15% vs 0.6%) and minor (3.7% vs 5.2%) bleeding events were observed with extended prophylaxis, and the all-cause mortality at 6 months did not differ significantly between groups. The final results of the trial are awaited, including subgroup analyses to determine specific populations in whom extended prophylaxis is most beneficial.

Quality Improvement Initiatives


Insights on the epidemiology of DVT were explored in this prospective analysis from 183 U.S. hospitals that used a registry of patients who had a DVT confirmed with ultrasonographic examination. There were no exclusion criteria. A total of 5451 surgical and medical patients were enrolled and were reclassified as having the DVT in either the in-hospital or outpatient setting. Diagnosis of symptomatic DVT was sooner if the patient was in the hospital (after 1 day of symptoms) compared with the outpatient setting (after 3 days of symptoms). Use of LMWH as a bridge to warfarin was the most common approach used in either setting for treatment. One of the most notable findings was that 71% of patients with a DVT had not received prophylaxis within the previous 30 days. However, it should be taken into account that presence of bleeding concerns and hesitation to use prophylaxis were not considered. Regardless, this large multicenter study clearly points out the need to improve VTE prophylaxis.

Tapson VF, Decousus H, Pini M, et al, for the IMPROVE Investigators. Venous thromboembolism prophylaxis in acutely ill hospitalized medical patients: findings from the international

This international observational study used a registry to assess how VTE prophylaxis was used in acutely ill medical patients. Data were abstracted after hospital discharge of 15,156 patients in 52 hospitals from 12 countries. Of note is that 55% of the 24,585 initially assessed patients were excluded from the analysis. Prophylaxis was administered in 61% of patients, with 52% and 43% of patients from the United States and other countries, respectively, receiving prophylaxis according to the ACCP guidelines in place at that time. In the United States, UFH was the most common form of prophylaxis compared with LMWH in other countries. Overall, this analysis points out the need to improve prophylaxis on a global basis.


Surgical procedures significantly increase the risk of developing VTE. Despite the overwhelming evidence, including numerous supporting trials, the use of VTE prophylaxis continues to be inadequate. The Surgical Care Improvement Project (SCIP) focuses on decreasing postoperative complications and improving postoperative outcomes. To minimize these risks, including postoperative VTE, the Centers for Medicare and Medicaid Services along with the Joint Commission have developed measures to ensure VTE prophylaxis was ordered (SCIP 1) and provided within 24 hours before and after surgery (SCIP 2). Additional measures are in development to assess the total number of hospitalized adult patients who had a subsequent admission within 30 days for conditions related to VTE. Health systems may need to expand management plans beyond the time the patient is within their sphere of influence, as the risk period for VTE may continue after discharge, to avoid both being penalized with reductions in pay-for-performance as well as having to internally cover the cost of care for the subsequent VTE. The Centers for Medicare and Medicaid Services have recently announced that it will no longer pay for hospital-acquired “never events,” including VTE after orthopedic surgery.


In 2005, the Joint Commission and the National Quality Forum collaborated on developing consensus standards for the prevention or care of VTE. The measures encompassed prevention, treatment, and outcomes. In the summer of 2008, the National Quality Forum endorsed six of the original 19 initial measures. Implementation of these measures is scheduled to occur in the fall of 2009. Among various requirements, these measures will encourage the provision of VTE prophylaxis during admission and at transfer into or out of the ICU. They will also require appropriate dosing and monitoring (including platelet counts) during UFH therapy. In addition, discharge instructions for individuals who developed VTE during hospitalization, and assessment of the rate of potentially preventable VTE will be required of all health care institutions.


The Joint Commission has recognized the importance of providing safety and quality of health care through various RR strategies. Anticoagulation therapy has been recognized as a source of frequent drug-related adverse events, many of which may cause harm to the patient. Starting in January 2009, National Patient Safe Goals 3E requires that all health care settings implement programs to ensure the safe use of anticoagulants. The nine goals encompass various aspects of the use and delivery of anticoagulants, as well as the education of providers and patients regarding antithrombotic therapy. Although only three classes of anticoagulants are currently targeted (UFH, LMWH, and warfarin), a comprehensive program will include defined programs for the use of direct thrombin inhibitors as well. This initiative has positioned the use of anticoagulation therapy as a critical issue for health systems and is resulting in the development of improved management programs across the United States.

The benefits of an electronic alerting system were evaluated in this observational analysis of patients randomly assigned to no intervention (1251 patients) and those whose managing physician received an electronic alert (1255 patients) regarding individualized risk of VTE and links to VTE prophylaxis guidelines and order sets. The use of mechanical (10.0% vs 1.5%, \( p<0.001 \)) or pharmacologic (23.6% vs 13.0%, \( p<0.001 \)) prophylaxis was higher when the physician was notified than when no notification was received. The primary end point was development of VTE at 90 days, which occurred in 4.9% of the intervention group versus 8.2% of the control group. Because the study was nonblinded, potential diagnostic bias cannot be excluded. Nevertheless, this study is the most robust of many intervention studies and suggests that alerting systems can improve the rate of VTE prophylaxis and lower the risk of clinical VTE.


This review explored strategies from 30 studies published between 1996 and 2003 that were used to improve VTE prophylaxis. Studies not showing a positive impact were excluded. Only one randomized controlled trial was located, with the remainder including audits related to implementation of a practice guideline or protocol. Adherence to guidelines in general was found to be consistently poor, with no more than 50% receiving prophylaxis. Higher VTE prophylaxis rates were observed when implementing an active or multiple strategy approach. Presence of an audit process and providing feedback or having an active reminder in place appeared to have the highest success rates. Because of the nature of how the assessments were conducted, notable bias could be present. The samples of the studies were not large enough to provide hard outcomes such as reduction in the rate of VTE. Nevertheless, the findings are significant, and the article provides an excellent review of the multiple studies that have evaluated various strategies to improve VTE prophylaxis rates.


The ACCP guidelines are considered to be a key document that guides approaches to VTE prophylaxis. In this retrospective report of a national data warehouse comprising data on 1.3 million hospitalized patients, by using selected International Classification of Diseases, Nine Revision codes, the compliance rate to the guidelines was assessed in individuals older than 40 years. Of the 123,304 admissions that met the inclusion and exclusion criteria, only a 13.3% compliance rate was noted. Compliance was higher in selected populations such as orthopedic surgery, but 16% or less in the remaining patients. Only 23.4% received some form of prophylaxis. These observations support the need for improved use of appropriate VTE prophylaxis, which is a focus of pending initiatives from the Joint Commission. Further, the SCIP guidelines, which have so far used the recommendations of the ACCP conference to define prophylaxis, will also create incentives for facilities to be compliant.

References