Why Thrombosis Prophylaxis Fails

Joseph A. Caprini, MD, MS, FACS, RVT

Abstract

Thrombosis prophylaxis methods have been widely tested and found to be extremely effective for the prevention of serious or fatal events known to be common in patients undergoing surgery or who are medically ill. A common reason for failure occurs when physicians apply inadequate measures due to a lack of awareness of the problem. Failure to perform individual risk assessment is another common reason for failure, since individuals may undergo a low-risk operation but have multiple risk factors dictating a much more robust approach to prophylaxis than group recommendations dictate. The presence of ongoing risk such as cancer or history of past venous thromboembolism (VTE) may dictate the use of prophylaxis following hospital discharge. Failure to provide this coverage often leads to serious or fatal events days or even weeks later. The use of aspirin for prophylaxis after orthopedic surgery is a weak, relatively ineffective approach to preventing the many faces of VTE, including clinical and asymptomatic VTE, pulmonary hypertension, paradoxical stroke and the post-thrombotic syndrome. Finally, failure to use combination physical and pharmacologic methods together in the highest-risk patients may lead to the development of VTE, which could be avoided with an appropriate combination approach.

Background

Venous thromboembolism (VTE) is a serious and often fatal disease affecting approximately 900,000 individuals in the United States each year, according to Heit et al.[1] They estimate that 296,000 deaths from pulmonary embolism (PE) occur, including 34% who present as sudden death. The inability of the clinician to help patients who die without warning is a frustrating problem. Many of these hospitalized patients had serious disease, and without an autopsy, often the true cause of death was never determined. One-third of these fatalities occurred following hospital discharge, which presents a difficult problem since resources are generally lacking for careful followup after discharge. It is uncommon to have autopsies performed in these individuals due to cost and other issues. Unfortunately, without accurate necropsy data, the true incidence of fatal PE or paradoxical stroke is difficult to determine. Heit et al developed an incidence-based model that included both hospital- and community-acquired VTE events, as well as death from recognized and unrecognized VTE.

A similar analysis of inpatients, using VTE criteria established by the American College of Chest Physicians (ACCP) estimated that more than 12 million patients are at risk for VTE.[2] A total of 7.7 million medical in-patients and 4.3 million surgical patients met ACCP guideline criteria for VTE risk, with VTE prophylaxis recommended.[2] Although the risk of deep vein thrombosis (DVT) is thought to be most commonly associated with surgical patients, 50–70% of symptomatic thromboembolic events and 70–80% of fatal PE occur in nonsurgical patients.[3] Approximately 10% of all hospital deaths are due to PE. Patients in the medical intensive care unit (ICU) are at particularly high risk for DVT. During an 8-month screening study, DVT was detected by ultrasound in 33% of 100 patients admitted to the medical ICU with an anticipated minimum stay of 48 hours.[4] It is unfortunate that these facts are not common knowledge among both physicians and the public.

Inadequate prophylaxis due to lack of awareness

Lack of awareness is a major reason for inappropriate or weak thromboprophylaxis use in many hospitalized patients. Failure of an inadequate thromboprophylaxis measure such as aspirin is one example and is not recommended by Chest or the International Consensus Guidelines.[5,6] The American Academy of Orthopedic Surgeons created a position statement that endorses the use of aspirin in some orthopedic patients, but these changes lack robust evidence-based guidelines documents.[7]

Failure to perform individual risk assessment

Another problem that affects the type and length of prophylaxis and fosters development of VTE is the lack of appropriate individual patient risk assessment. Many years ago, when there were no ultrasound, computed tomographic (CT) or magnetic resonance imaging (MRI)

From the Division of Vascular Surgery, NorthShore University Health System, Evanston, Illinois, Northwestern University Feinberg School of Medicine, Chicago, Illinois, and the Robert R. McCormick School of Bioengineering Northwestern University, Evanston, Illinois.

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Address for correspondence: Joseph A. Caprini, MD, MS, FACS, Louis Biegler Professor of Surgery, Division of Vascular Surgery, NorthShore University Health System, Coventry Road, Northfield, IL 60093. E-mail: jcaprini2@aol.com

Table 1. A system of scoring that involves eliciting from the patient all of the established risk factors that have been associated with developing a VTE (Table 2 allows for the prediction of risk with the resulting score).

Risk Factors (1 point)
- Age 40–59 years
- Minor surgery
- Previous major surgery (1 month)
- Varicose veins
- Inflammatory bowel disease
- Current leg swelling
- Obesity (BMI 30–40)
- Acute myocardial infarction (1 month)
- Congestive heart failure (1 month)
- Sepsis (1 month)
- Serious lung disease including pneumonia (1 month)
- Chronic obstructive pulmonary disease (COPD)
- Leg plaster cast or brace
- Current bedrest
- Central venous or PICC line
- Blood transfusion (1 month)
- Oral contraceptives or hormonal replacement therapy
- Pregnancy or postpartum (1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (3 or more), premature birth with toxemia or growth-restricted infant

Risk Factors (2 points)
- Age 60–74 years
- Major surgery (> 60 minutes)*
- Arthroscopic surgery (> 60 minutes)*
- Laparoscopic surgery (> 60 minutes)*
- Previous malignancy
- Morbid obesity (BMI > 40)

Risk Factors (3 points)
- Age ≥ 75 years
- Major surgery (2–3 hours)*
- BMI > 50 (venous stasis syndrome)
- History of SVT, DVT/PE
- Family history of DVT/PE
- Present cancer or chemotherapy
- Positive Factor V Leiden or prothrombin 20210A
- Hyperhomocysteinemia
- Positive ACA antibodies/lupus anticoagulant
- Heparin-induced thrombocytopenia
- Other

Risk Factors (5 points)
- Elective major lower-extremity arthroplasty
- Hip, pelvis, or leg fracture (< 1 month)
- Stroke (< I month)
- Multiple traumas (< 1 month)
- Acute spinal cord injury/paralysis (< I month)
- Major surgery lasting > 3 hours*

**Select only one from the surgery category*

scanners, clinicians performed thorough history and physical examinations. Today the trend is to provide prophylaxis by groups and not perform individual risk assessment. This approach is endorsed by the current Chest guidelines.[5] However, the guidelines can truly only apply to patients with the same characteristics as the clinical trial population. Many patients we see in daily clinical practice would be excluded from those trials, but still require care. The physician must tailor a plan of care based on the unique risk of a particular patient by combining knowledge of the literature with clinical experience, logic and emotion (that is, the practice of medicine). One example would be a 43-year-old female who had repair of a ruptured Achilles tendon and postoperatively was placed in a cast and was on crutches. She had active inflammatory bowel disease (IBD) and was taking estrogen for birth control. She was given prophylaxis at the time of surgery, but anticoagulants were not recommended after discharge. Six weeks later, while still in the cast, she developed a fatal PE. She had received prophylaxis briefly, but because of her multiple risk factors, the prophylaxis should probably have been continued. Unfortunately, there are no trials in patients with her unique combination of risk factors, since no institutional review board would approve a study where patients who were potentially "at risk" would be placed in a control group. Since she had seven risk factors including leg injury, leg surgery, estrogens, leg cast, relative immobility, IBD and age over 40, her chance of developing VTE was nearly 100%.[8] Such patients require prophylaxis for the entire period they are at risk for VTE.[9] Guidelines indicate that patients with > 4 risk factors have up to a 5% mortality risk without appropriate prophylaxis.[5] The administration of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) prophylaxis reduces the fatal PE rate to 0.15%.[10] Hence, the therapeutic plan for this patient would have been administration of appropriate anticoagulation until she was walking normally. Had that been the case, she might still be alive, although she may have suffered a nonfatal event requiring treatment.

Prophylaxis that is inadequate often fails in the medically ill patient. An example would be a 78-year-old male in the hospital on bedrest with pneumonia. The patient may have been given UFH 5,000 units twice daily or graduated compression stockings. However, both of these strategies in the medically ill population are associated with a high failure rate, as patients develop VTE despite these measures.[11] Individual risk assessment would place this patient at extreme risk. A lower dose of heparin or stockings alone are likely to fail, although technically it is prophylaxis.[11] However, giving heparin every 8 hours along with intermittent pneumatic compression (IPC) would be justified. Studies have shown that UFH every 8 hours is more effective than every 12 hours, although the risk of bleeding is higher.[12] It has also been shown that combining

Table 2.[3,15] The elicited score (see Table 1) can be used to predict the risk of an individual patient having a clinically evident, imaging-proven VTE during or following discharge

Score	Incidence of DVT*	Risk Level	Prophylaxis
0–1	0.00%	Low	No specific measures
2	0.70%	Moderate	Physical or pharmacologic
3–4	0.97%	High	Pharmacologic
5 or more†	1.94%	Highest	Physical + pharmacologic

Clinically evident, imaging-proven VTE.
†Out-of-hospital pharmacologic prophylaxis may be appropriate.

IPC with anticoagulants increases efficacy without increasing bleeding in the medically ill patient.[13]

We use a system of scoring that involves eliciting from the patient all of the established risk factors that have been associated with developing a VTE (Table 1). Each factor is weighted according to the likelihood of that factor causing a VTE.[14] The resulting score can be used to predict the risk of an individual patient having a clinically evident, imaging-proven VTE during or following discharge (Table 2). Data from the National Surgical Quality Improvement Project (NSQIP) sponsored by the American College of Surgeons have validated this concept.[15] The system is widely used and several investigators have employed this concept of scoring in different clinical settings.[16-21] The method is far from perfect, but provides a guide to the clinician. In some cases where the incidence of post-discharge VTE is high, continued prophylaxis following discharge can be justified and help prevent thrombosis.

Failure to provide extended prophylaxis

Medical patients with ongoing risk benefit from extended prophylaxis, as was shown in a multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial in 5,049 patients that compared extended-duration (28 days) prophylaxis with LMWH and the standard regimen of LMWH given during hospitalization. The rates of all VTE events and symptomatic or asymptomatic events were significantly reduced with extended prophylaxis versus standard-duration prophylaxis. Major bleeding occurred in 12 patients receiving extended LMWH and in 3 patients receiving the short-duration prophylaxis (0.6% vs. 0.1%; $p = 0.0192$).[22] Studies in surgical patients have also revealed that failure to provide extended prophylaxis to those at risk results in a significant late incidence of VTE. Agnelli and colleagues undertook a prospective observational study of 2,373 surgical patients to evaluate the incidence of clinically overt VTE and to identify risk factors for VTE. Thirty percent of patients received post-discharge VTE prophylaxis compared to 81.8% during hospitalization. In the study, 40% of VTE and PE events occurred more than 21 days after surgery, leading researchers to conclude that there is a need to extend antithrombotic prophylaxis beyond hospital discharge and the conventional perioperative period.[23]

Inadequate prophylaxis following major orthopedic surgery

Although there have been advances in understanding the incidence, pathophysiology and benefits of VTE prophylaxis post major orthopedic surgery, and guidelines for prophylaxis have been established, there remains a portion of the total hip replacement (THR), total knee replacement (TKR), and hip fracture repair (HFR) population that does not receive adequate VTE prophylaxis. To establish a better understanding of the current practices of prophylaxis implementation, Stratton et al performed a retrospective review of the medical charts of 1,907 patients from 10 teaching or community-based hospitals. These patients were randomly selected from the patient population that underwent high-risk major abdominal surgery, TKR, THR or HFR from January 1996 to February 1997. The percentage of patients who received Grade A VTE prophylaxis in accordance with recommendations of the ACCP guidelines was 84.3% in the THR group, 45.2% in the HFR group and 76% in the TKR group. In the THR, HFR and TKR groups, 8.4%, 46.4% and 22.6% of patients, respectively, received some form of prophylaxis. However, the prophylaxis given did not comply with ACCP guidelines. Only 7.3%, 8.4% and 1.5% in the THR, HFR and TKR groups, respectively, received no prophylaxis whatsoever. Prophylactic therapies prescribed at discharge were most common in the TKR group (70.2%). Patients in the THR and HFR groups were only given prophylactic therapy approximately 50% of the time.[24]

In their meta-analysis of randomized trials, Eikelboom et al found a significant reduction in the incidence of asymptomatic DVT among THR or TKR patients receiving extended-duration prophylaxis with LMWH or UFH (9.6% of treated patients vs. 19.6% of controls; $p \leq 0.001$)[25] The authors concluded that among patients undergoing THR or TKR, extended-duration prophylaxis significantly reduces the frequency of symptomatic VTE. The reduction in risk is equivalent to about 20 symptomatic events per 1,000 patients treated. Geerts et al reviewed studies of the incidence of symptomatic DVT or PE in patients undergoing THR or TKR who received extended prophylaxis with LMWH or warfarin. Symptomatic DVT/PE occurred in 1–3% of patients and fatal PE in < 1% of patients receiving extended prophylaxis.[3]

Extended therapy as a means of prophylaxis: Evidence-based guidelines

Evidence-based medicine guidelines based on venographic endpoints recommend in-hospital prophylaxis with LMWH in patients undergoing elective hip surgery. Emerging data suggest that out-of-hospital use may offer additional protection; however, uncertainty remains about the risk-benefit ratio. To provide clinicians with a practical pathway for translating clinical research into practice, a systematic review of trials comparing extended out-of-hospital LMWH prophylaxis versus placebo was conducted. Compared with placebo, extended out-of-hospital prophylaxis decreased the frequency of all episodes of DVT (placebo rate, 150/666 patients [22.5%]; relative risk [RR], 0.41; 95% confidence interval [CI], 0.32–0.54; $p < 0.001$), proximal venous thrombosis (placebo rate, 76/678 patients [11.2%]; RR, 0.31; CI, 0.20–0.47; $p < 0.001$), and symptomatic VTE (placebo rate, 36/862 patients [4.2%]; RR, 0.36; CI, 0.20–0.67; $p = 0.001$). Major bleeding was rare, occurring in only 1 patient in the placebo group. Extended LMWH prophylaxis showed consistent effectiveness and safety in the trials (regardless of study variations in clinical practice and length of hospital stay) for venographic DVT and symptomatic VTE.[26–29] These findings support the need for extended out-of-hospital prophylaxis in patients undergoing hip arthroplasty surgery. These observations underscore the relation between venographic and symptomatic VTE events. This evidence, along with numerous other studies, has convinced us to treat the highest-risk patients with a thrombosis prophylaxis regime that has been shown to be superior both clinically and venographically.

In an excellent study examining the efficacy of fondaparinux for thromboprophylaxis in high-risk hip fracture patients, patients received fondaparinux 2.5 mg for 7 days following surgery; 656 patients were randomized double-blind to receive placebo or continue the fondaparinux regimen for 21 additional days. Primary efficacy was VTE based on bilateral venography. Total VTE was 1.4% for extended prophylaxis and 35% for short-term prophylaxis ($p = 0.001$), with a relative risk reduction (RRR) of 96%.[30] The authors reported that although there was a trend toward more major bleeding in the fondaparinux group than in the placebo group ($p = 0.06$), there were no differences between the two groups in the incidence of clinically relevant bleeding (leading to death, reoperation or critical organ bleeding). They further concluded that extended prophylaxis with fondaparinux for 3 weeks after hip-fracture surgery reduced the risk of VTE by 96% and was well tolerated. The patients who received the drug over the short term experienced an 8.3% incidence of positive venograms done 7–10 days postoperatively.[31] If the venogram was delayed for 28–35 days, the venographic incidence of DVT was 35%. What a dramatic illustration of the value of extended prophylaxis in the very-high risk orthopedic patient! These studies also provide further proof that many VTE events can occur weeks after discharge.

Abdominal surgical patients with cancer form another important group where the value of out-of-hospital prophylaxis has been demonstrated using venography. Bergqvist evaluated 332 patients undergoing surgery for cancer who received enoxaparin for 6–10 days after surgery and then were randomized to enoxaparin or placebo for another 21 days.[2] The incidence of all VTE events at 21 days was 12.0% with placebo and 4.8% with enoxaparin ($p = 0.02$), and this benefit persisted to 3 months ($p = 0.01$). No differences were observed in the incidence of bleeding or complications.[32] Rasmussen reported the results of a multicenter randomized trial of short-term versus long-term dalteparin thromboprophylaxis after major abdominal surgery in 590 patients. The venographic incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis (29/178 patients) to 7.3% after prolonged thromboprophylaxis (12/165) (RRR 55%; 95% CI, 15–76; $p = 0.012$). Bleeding events were not increased with prolonged compared to short-term thromboprophylaxis.[33] Thus, we have another study with a different LMWH that shows the value of prolonged prophylaxis after major abdominal surgery in patients with cancer.

Combination prophylaxis for the highest-risk patients

The value of combining IPC with anticoagulants has been known for over 25 years since the results of Maxwell Borow were first published. This careful investigator was significantly ahead of his time. The following is a quote from his studies in surgical patients. "Worldwide statistics reveal that 25 to 40 percent of patients who are over the age of 40 years and operated on for 1 or more hours will develop a deep venous thrombosis (DVT). The studies reviewed in this paper were performed to evaluate several modalities and compare their effectiveness in preventing DVT in postoperative patients. In the first study, five modalities plus a control group were evaluated in 562 patients from five surgical specialties. The incidence of DVT in the control group was 35 percent. Though most of the pharmacologic agents were effective in reducing the incidence of DVT, the antistasis devices (gradient elastic stockings and intermittent pneumatic compression) were most effective. The purpose of the second study was to evaluate the effectiveness of combining a pharmacologic drug with an antistasis modality. Deep venous thrombosis was virtually eliminated in this group of 328 patients. There was only a 1.5 percent incidence of DVT in the treated population as compared to a 26.8 percent incidence in the control group. Thus, it seems that combining one antistasis and one pharmacologic agent greatly reduces the incidence of lower extremity thrombi. I-125 fibrinogen scanning was the most sensitive test in detecting DVT and had an accuracy of 97 percent."[34] It is fascinating that in 2007 the APOLLO

trial reported a 1.5% incidence of DVT in patients receiving IPC plus fondaparinux.[35] This study was performed in abdominal surgery patients, and included both gallbladder and hernia operative procedures. Forty percent of the patients had cancer, and the comparator was IPC and a saline placebo-blinded injection. Ramos, in 1996, reported on a consecutive group of 2,500 cardiac surgery patients undergoing coronary artery bypass over a 10-year period. He found that the incidence of proven PE was 1.4% in the UFH plus IPC group compared to heparin alone (4%). This represented a 62% reduction in PE that was highly statistically significant ($p < 0.001$).[36] Failure of clinicians to employ combined prophylaxis in the highest-risk patients is, in our opinion, a significant reason for failure of prophylaxis.

Conclusion

There are many reasons for the failure of prophylaxis to prevent a VTE event. One essential ingredient for success is to perform a careful history and physical on every patient to assess their unique risks for thrombosis. It is also essential to use appropriate prophylaxis alone or in combination for the entire period the patient is at thrombotic risk. The use of out-of-hospital prophylaxis in many situations is important to reduce the overall morbidity and mortality of this serious disease.

References

1. Heit JA, Cohen AT, Anderson FAJ, on behalf of the VTE Impact Assessment Group. Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US. *ASH Annual Meeting Abstracts* 2005;106:910.
2. Anderson FA Jr, Zayaruzny M, Heit JA, et al. Estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism. [see comment]. *Am J Hematol* 2007;82:777–782.
3. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:338S–400S.
4. Hirsh DR. Venous thromboembolism in hospitalized patients. *JAMA* 1995;274:335–337.
5. Geerts WH, Pineo GF, Heit JA. Prevention of venous thromboembolism: The Eighth ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2008;133:381S–453S.
6. Nicolaides AN. International consensus guidelines. *Int Angiol* 2006;25:101–161.
7. AAOS. American Academy of Orthopaedic Surgeons Clinical Guideline. November 2007. Available at http://www.aaos.org/research/guidelines/guide.asp. Accessed February 23, 2009.
8. Anderson FA Jr, Spencer FA, Anderson FA Jr, et al. Risk factors for venous thromboembolism. *Circulation* 2003;107:I9–I16.
9. Anderson FA Jr, Wheeler HB, Anderson FA Jr, et al. Venous thromboembolism. Risk factors and prophylaxis. *Clin Chest Med* 1995;16:235–251.
10. Haas S, Wolf H, Kakkar AK, et al. Prevention of fatal pulmonary embolism and mortality in surgical patients: A randomized double-blind comparison of LMWH with unfractionated heparin. *Thromb Haem* 2005;94:814–819.
11. Goldhaber SZ, Dunn K, MacDougall RC, et al. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. [see comment]. *Chest* 2000;118:1680–1684.
12. King CS. Prevention of VTE comparing twice daily vs. three times daily unfractionated heparin in the medically ill: A meta-analysis. *Chest* 2007;131:507–516.
13. Kamran SI, Downey D, Ruff RL, et al. Pneumatic sequential compression reduces the risk of deep vein thrombosis in stroke patients. *Neurology* 1998;50:1683–1688.
14. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon* 2005;51:70–78.
15. Bahl V, Hu H, Henke PK, et al. A validation study of a retrospective venous thromboembolism risk scoring method. Submitted for publication 2009.
16. McLafferty RB, Lohr JM, Caprini JA, et al. Results of the national pilot screening program for venous disease by the American Venous Forum. *J Vasc Surg* 2007;45:142–148.
17. McLafferty R, Passman M, Caprini J. Increasing awareness about venous disease: The American Venous Forum expands the National Venous Screening Program. *J Vasc Surg* 2008;48:394–399.
18. Osborne NH, Wakefield TW, Henke PK. Venous thromboembolism in cancer patients undergoing major surgery. *Ann Surg Oncol* 2008;15:3567–3578.
19. Seruya MS, Venturi ML, Iorio ML, et al. Efficacy and safety of venous thromboembolism prophylaxis in highest risk plastic surgery patients. *J Plastic Reconstr Surg* 2008;122:1701–1708.
20. Zakai NA, Wright J, Cushman M. Risk factors for venous thrombosis in medical inpatients: Validation of a thrombosis risk score.[see comment]. *J Thromb Haem* 2004;2:2156–2161.
21. O'shaunnessey D. Evaluating the performance of a previously reported risk score to predict venous thromboembolism. A verity registry study. *Blood* 2006;108:716.
22. Hull R. Extended duration of anticoagulation in the medically ill. XXIST Congress of the International Society on Thrombosis and Haemostasis. Geneva, Switzerland 2007:s001.
23. Agnelli G, Bolis G, Capussotti L, et al. A clinical outcome-based prospective study on venous thromboembolism after cancer surgery: The @RISTOS project. [see comment]. *Ann Surgery* 2006;243:89–95.
24. Stratton MAP, Anderson FAP, Bussey HIP, et al. Prevention of venous thromboembolism: Adherence to the 1995 American College of Chest Physicians consensus guidelines for surgical patients. *Arch Intern Med* 2000;160:334–340.
25. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: A meta-analysis of the randomised trials. [see comment]. *Lancet* 2001;358:9–15.
26. Bergqvist D, Benoni G, Bjorgell O, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement.[see comment]. *N Engl J Med* 1996;335:696–700.
27. Planes A, Vochelle N, Mazas F, et al. The use of enoxaparine in preventing deep venous thrombosis following total hip prosthesis. Randomized multicenter prospective trial. *Rev Chir Orthop Reparatrice Appar Mot* 1988;74(Suppl 2):215–218.
28. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs. in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: A double-blind, randomized comparison. North American Fragmin Trial Investigators.[see comment]. *Arch Intern Med* 2000;160:2208-2215.
29. Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. [see comment]. *J Bone Joint Surg Am* 2001;83A:336–345.
30. Eriksson BI, Lassen MR, Investigators PEiH-FSP. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: A multicenter, randomized, placebo-controlled, double-blind study. [see comment]. *Arch Intern Med* 2003;163:1337–1342.
31. Eriksson BI, Bauer KA, Lassen MR, Turpie AG, Steering Committee of the Pentasaccharide in Hip-Fracture Surgery. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. [see comment]. *N Engl J Med* 2001;345:1298–1304.
32. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002;346:975–980.
33. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: A multicenter randomized open-label study. *J Thromb Haem* 2006;4:2384–2390.
34. Borow M, Goldson HJ, Borow M, et al. Prevention of postoperative deep venous thrombosis and pulmonary emboli with combined modalities. *Am Surg* 1983;49:599–605.
35. Turpie AG, Bauer KA, Caprini JA, et al. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: A randomized, double-blind comparison. *J Thromb Haem* 2007;5:1854–1861.
36. Ramos R, Salem BI, De Pawlikowski MP, et al. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery.[see comment]. *Chest* 1996;109:82–85.