Why Thrombosis Prophylaxis Fails

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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. 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. 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. 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. 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. 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. 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.

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)
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 (< 1 month)
- Multiple traumas (< 1 month)
- Acute spinal cord injury/paralysis (< 1 month)
- Major surgery lasting > 3 hours*

*Select only one from the surgery category
IPC with anticoagulants increases efficacy without increasing bleeding in the medically ill patient.12

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.13 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.14 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; $p < 0.001$).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

### Table 2

<table>
<thead>
<tr>
<th>Score</th>
<th>Incidence of DVT$^*$</th>
<th>Risk Level</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>0.00%</td>
<td>Low</td>
<td>No specific measures</td>
</tr>
<tr>
<td>2</td>
<td>0.70%</td>
<td>Moderate</td>
<td>Physical or pharmacologic</td>
</tr>
<tr>
<td>3–4</td>
<td>0.97%</td>
<td>High</td>
<td>Pharmacologic</td>
</tr>
<tr>
<td>5 or more†</td>
<td>1.94%</td>
<td>Highest</td>
<td>Physical + pharmacologic</td>
</tr>
</tbody>
</table>

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

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. 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%. 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. 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. 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. 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. 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.” It is fascinating that in 2007 the APOLLO
trial reported a 1.5% incidence of DVT in patients receiving IPC plus fondaparinux.\textsuperscript{31} 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 ($p < 0.001$).\textsuperscript{32} 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**


