Author Queries

BOOK: LABROPOULOS

CHAPTER NUMBER: 14

Q1 Please check the inserted short title
Q2 Please provide key to abbreviation for Table 1,2,6,7,8.
Q3 Is this figure part of table 4? Can it be placed below table text?.
Q4 Please note the references are not cited in sequential order. Please confirm if it is okay.
Q5 Please confirm 2400 days is ok
Q6 Please provide a minimum of three author names for all the et al. references.
Q7 Please provide complete author name for the second author
Q8 Please provide updated and complete details.

14
Venous Thrombosis Prophylaxis

Joseph A. Caprini
Feinberg School of Medicine, Northwestern University, Chicago, Illinois, U.S.A.
Evanston Northwestern Healthcare, Evanston, Illinois, U.S.A.
Glenbrook Hospital, Glenview, Illinois, U.S.A.

Dereck Wentworth
U.S. Medical Affairs, New York, U.S.A.

INCIDENCE AND MAGNITUDE OF THE PROBLEM

Venous thromboembolism (VTE) is a leading cause of mortality in the United States and causes more deaths than AIDS, breast cancer, and motor vehicle crashes combined. Pulmonary embolism (PE) is responsible for up to 200,000 fatalities annually in the United States, while in 2002 AIDS-related deaths were seen in 14,095 individuals (1). Breast cancer-related fatalities for the year 2002 were estimated to be 41,883 patients (2), while U.S. highway fatalities that same year were 44,065 individuals (3). The in-hospital case fatality rate attributed to venous thromboembolic disease is 10–25% in the United States. Elderly patients suffering pulmonary emboli have a case fatality rate of 15% at 28 days, while cancer patients have a 25% fatality rate at 28 days. By one year elderly VTE victims suffered a mortality rate of 21% and cancer patients 39% (1,4,5). Most of these studies underestimate the incidence of VTE because of low autopsy rates of 10–20%, outpatient cases were not counted, and long-term care facility data were not considered. The actual mortality from VTE is probably higher, but unfortunately, unlike breast cancer and AIDS, the National Center for Health Statistics does not track deaths due to VTE.

Surgical patients have been well-studied and their risk for VTE is known. In patients undergoing total hip replacement who do not have additional risk factors and do not receive prophylaxis, the incidence of fatal PE is 0.2% to 0.5%. Patients who undergo surgery for fractured hips and do not receive prophylaxis may suffer a 2.5% to 7.5% incidence of fatal PE (6). Risk factors associated with acute inpatient mortality following orthopedic surgery were evaluated in 43,215 patients. Conditions identified preoperatively related to mortality included chronic renal failure, congestive heart failure, cancer with bone metastasis, COPD, atrial fibrillation, and age over 70 years. Procedural factors influencing mortality were found to be surgery for trauma or hip fracture, with a mortality rate five times higher than other procedures. Mortality rates from postoperative complications were 27.6% from renal failure, 19.3% from

LABROPOULOS—CH 14—11/1/2006—189461—XML MODEL C – pp. 177–200

pulmonary embolus, 19.3% from myocardial infarction, and 8.6% each for cerebrovascular accidents and pneumonia (7). One of the important lessons learned from this study is that mortality from surgical procedures is frequently caused by pulmonary embolism, certain surgical procedures are higher risk than others, and preoperative patient factors also affect risk of VTE. This indicates that the choice of VTE prophylaxis should take into account all of these factors.

Surgical patients are not the only ones at risk for VTE. The incidence of thrombosis in patients admitted to the hospital on the medical service averages 10% to 20% overall. Patients admitted with stroke have up to a 56% incidence of DVT and those admitted to the medical intensive care unit have a rate of DVT between 28% and 33% (8–10). Patients at risk are those who have COPD, CHF, pneumonia, and inflammatory bowel disease. Large randomized prospective trials in the medical population have been done and consistently demonstrate an incidence of DVT between 10% to 20% in patients who receive no prophylaxis (11,12).

Patients undergoing colorectal surgery have a high incidence of VTE due in part to the long duration of surgery, pelvic resection, and the presence of cancer and/or inflammatory bowel disease. In a series of 20,000 patients in this category, 1.8% died of fatal pulmonary embolism despite receiving low-dose unfractionated heparin prophylaxis. The risk of PE in untreated patients is approximately 5% (13). The incidence of DVT in 12 general surgical trials was 22% in untreated surgical subjects, while it was seen in 29% of patients undergoing colorectal procedures (14).

There are a number of important reasons to provide thrombosis prophylaxis to patients who are at risk for VTE, as seen in Table 1. Prandoni and others have provided T1
data regarding the long-term clinical course of acute DVT. In approximately 5% of patients, DVT will recur within three months, in 18% at two years, and by eight years following the acute event, about 30% of individuals will suffer a second DVT (15–17).

The post-thrombotic syndrome (PTS) is estimated to occur in about 25% of patients following a first episode of DVT. This syndrome is characterized by the development of leg swelling, skin pigmentation, rashes, and in approximately 4% of individuals, an open ulcer. PTS can develop in patients with asymptomatic DVT, while recurrent ipsilateral DVT and proximal DVT will increase the risk of developing the syndrome. PTS also takes time to develop, with only 23% of post-thrombotic cases presenting within two years of the acute DVT (16). After such a long time, symptoms of recurrent VTE and PTS are not often attributed to a previous operative procedure or hospitalization for illness. One startling fact about the post-thrombotic syndrome is that 7% of patients are disabled by this

Table 1 Rationale for VTE Prophylaxis

Prevent fatal pulmonary emboli
1–5% incidence in patients with >4 risk factors
16.7% mortality at 3 mo
Prevent clinical venous thromboembolism
Morbidity—months of anticoagulation, tests, hose, changes in lifestyle
Prevent silent venous thromboembolism
Risk of subsequent event double that of control population (Borrow)
Prevent embolic stroke in those with patent foramen ovale
20–30% PFO rate; 50% disabled; 20% die; 30% recover
Prevent the post-thrombotic syndrome Q2
25% incidence following DVT and 7% severe
May not be evident for 2–5 yr

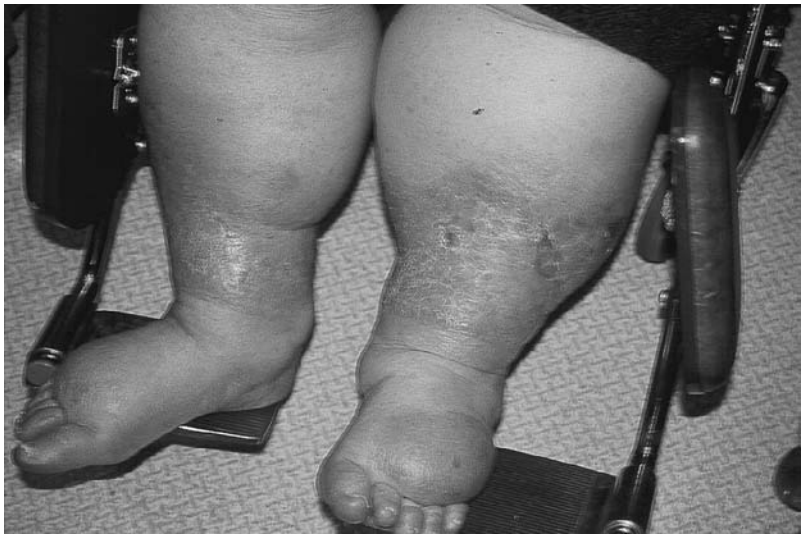


Figure 1 An example of severe post-thrombotic syndrome (PTS) post–hip arthroplasty. This woman demonstrates lymphedema, discoloration, pain, ulceration and obviously is severely debilitated by her condition.

condition and if a person develops recurrent DVT, the risk of the post-thrombotic syndrome is increased by six-fold (18).

The American Venous Forum has published an excellent classification of venous problems called the CEAP score, which helps classify the severity of changes in individual patients. Figure 1 shows a woman with severe post-thrombotic changes combined with F1
lymphedema. This is a very difficult picture as far as treatment is concerned and is definitely a permanent problem. It has been estimated that in the United States 2 million workdays are lost annually and 15 million Americans suffer from this problem (19). The cost of care for these problems in the United Kingdom is estimated at 400 million pounds annually and $300 million in the United States (8). The syndrome represents one of the most compelling arguments for effective thrombosis prophylaxis in all medical and surgical patients at risk, as it is much easier to prevent VTE than it is to treat PTS.

Another problem that is poorly recognized and very difficult to assess is the incidence of recurrent thromboembolism in patients who have had a subclinical event and later are at risk because of an operation or medical illness. Borow reported on 500 patients who underwent surgical procedures lasting an hour or more, were over the age of 40 years, and were studied postoperatively with fibrinogen scans and confirmed with contrast venography (20). He found that 66% of patients who had a history of venous thrombosis developed thrombosis postoperatively. He also reported that 50% of the patients with a significant medical history, including previous abdominal or leg surgery, trauma to the lower abdomen, or long bone fracture, developed postoperative venous thrombosis. Table 2 is a list of various signs, symptoms and clinical findings that may be associated T2
with a venous thromboembolic event. Obviously, all of these problems do not end with a fatality but that does not diminish the importance of the presence of these abnormalities as a clue to signal a possible VTE event.

We frequently encounter successful, busy clinicians who dispute the above data, usually saying that "in our practice we just don't see these problems." We would emphasize that in this modern era, autopsies are difficult to obtain; without them, the true

Table 2 Non Specific Signs and Symptoms of VTE

Leg pain	Leg swelling
Chest pain	Shortness of breath
Transient orthostatic hypotension	Narcotic excess
Fainting spell	Hypoxia
Patient readmission 90 days postoperatively	Postoperative pneumonia
Patient death 90 days postoperatively	Sudden death
Suspected MI	Death without autopsy
Patent foramen ovale	Post-thrombotic syndrome 5 yr postoperatively
Postoperative stroke	Failure to thrive

incidence of venous thromboembolic problems associated with clinical fatalities is impossible to calculate. Another modern problem in the United States is delivery of health care. When patients are discharged from the hospital after surgery or acute medical illness, they often may not be readmitted to the same hospital to treat a post-discharge VTE event. If these people develop venous thromboembolic complications, how is the busy clinical practitioner able to find out about these problems unless the patients' activities and whereabouts following discharge are carefully documented? We would remind those clinicians who are skeptical about the incidence and clinical significance of venous thromboembolic problems that the data are real and have been derived from hundreds of references. The thrombosis prophylaxis chapter in the latest Chest Consensus Conference on Antithrombotic Therapy contains 797 references that are the scientific basis for the incidence, morbidity and mortality associated with venous thromboembolic disease (6).

RISK ASSESSMENT

Some of us feel that the single most important aspect of thrombosis prophylaxis in medical and surgical patients is a careful, detailed risk analysis of each individual patient, being careful not to miss any important risk factors. One might say that this process is the medical equivalent of the preflight cockpit checklist for a commercial airliner. It would be unthinkable to fly without checking every possible item on the list to ensure the safety of the passengers and crew. We are indebted to the Chest Consensus Conference Guidelines that now have been published for the seventh time and give us clear direction regarding risk factors and their importance in the prevention of VTE. A number of formal risk assessment models are available for this purpose (21,22). Many feel that these are cumbersome and have not been adequately validated (6). Furthermore, clinicians find them cumbersome to implement in their routine practice. The consensus group suggests a simplified approach, categorizing patients into four different categories depending on their age, type of surgery, and presence of additional risk factors (Table 3). This is intended to T3 provide a uniform approach to a population of patients; however, we encounter daily situations where a low-risk procedure is performed on a patient at very high risk for VTE. It is true that in these very-high-risk individuals maximum prophylaxis will be used, so one could ask why all risk factors must be listed. There is considerable literature to suggest that patients with large numbers of risk factors may be at enormous risk for developing a postoperative venous thromboembolic event (6,8,23,24). If the patient is undergoing a quality-of-life procedure and falls into this category, we feel that part of the preoperative informed consent process should be to advise the patient of the degree of risk so the patient can decide on the importance of the procedure given the risks involved as assessed.

Table 3 Risk of VTE and Therapy Recommendations

Level of patient risk	DVT (%)		PE (%)		Recommended therapy
	Calf	Proximal	Symptomatic	Fatal	
Low					
Age under 40 yr Minor surgery No other RF	2	0.4	0.2	0.002	Aggressive mobilization
Moderate					
Minor surgery and additional RF Minor surgery, 40–60 yr and no additional RF Major surgery, <40 yr with no additional RF	10–20	2–4	1–2	0.1–0.4	LDUFH q12 h, LMWH, GCS, IPC
High					
Minor surgery in patients >60 yr or w/additional RF Major surgery in patients >40 yr or w/additional RF	20–40	4–8	2–4	0.4–1.0	LMWH, LDUFH q8 h, IPC
Very high					
Major surgery in patients >40 yr plus prior VTE, cancer, or hypercoaguable state Hip or knee arthroplasty, hip fracture surgery Major trauma, spinal cord injury	40–80	10–20	4–10	0.2–5	LMWH, fondaparinux, oral VKA, adjusted UFH, IPC/GCS + LDUFH/LMWH

Abbreviations: RF, risk factors; LMWH, low molecular weight heparin; VKA, Vitamin K antagonists; LDUFH, low dose unfractionated heparin; IPC, intermittent pneumatic compression; GCS, graduated compression stockings.
Source: Adapted from Ref. 6.

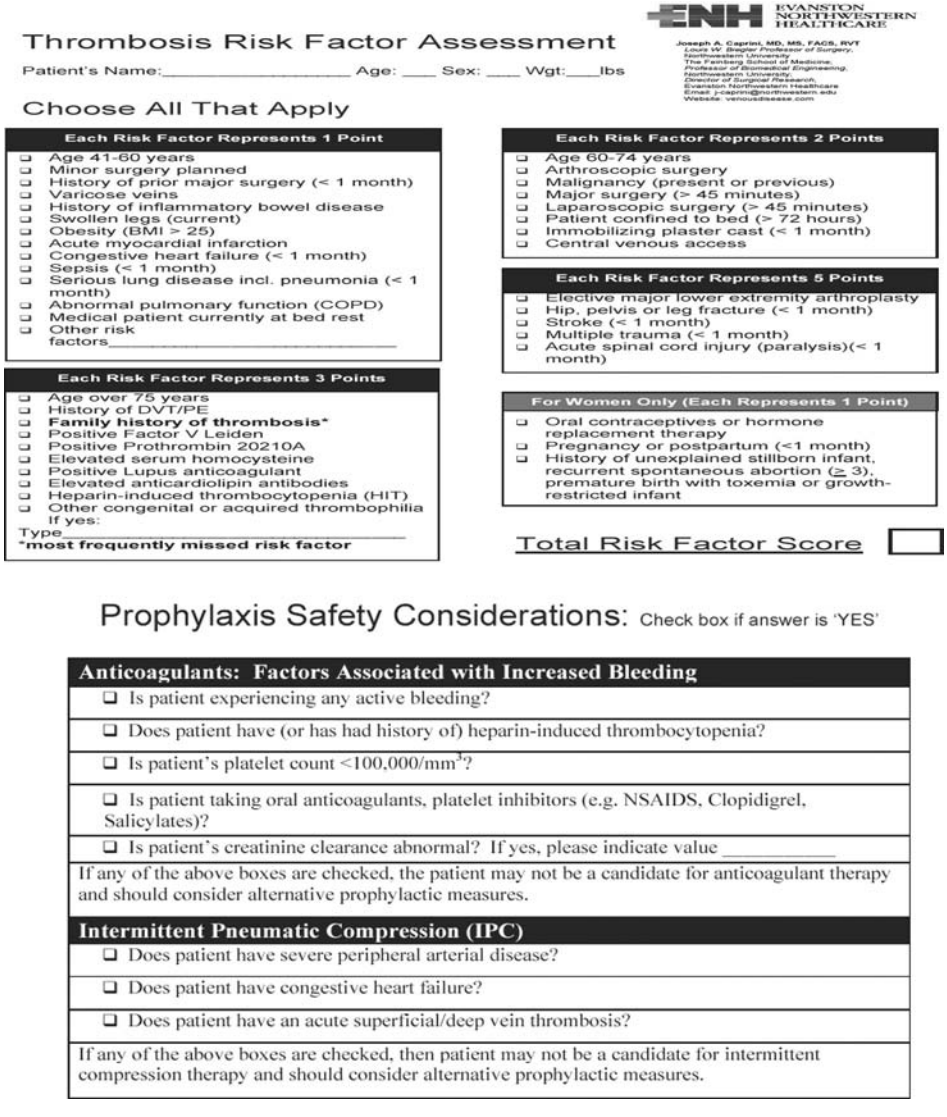
For example, if a patient with a heterozygous Factor V Leiden defect also has a protein C or S defect, the incidence of thrombosis may be as high as 70% to 90% (25). That may be too much of a chance to take for an elective quality-of-life procedure. Even with proper prophylaxis, VTE may still occur (the event rate is not zero), or they might experience excessive bleeding requiring withdrawal of prophylaxis, thus exposing the patient to a high risk of severe or fatal events. Without a complete preoperative risk assessment, how would one know which patients are in this category and need this extra counseling and decision-making analysis preoperatively?

We have developed a risk assessment form that has been used in our clinic for more than 15 years and is provided in Table 4. It consists of a point system linking the patient to the risk factor schema proposed by the Chest Consensus Guidelines (see Table 3). The use

Table 4 Recommendations for Therapy Based on Full Patient Risk Assessment

Total risk-factor score	Incidence of DVT	Risk level	Prophylactic regimen
0–1	<10%	Low	No specific measures, early ambulation
2	10–20%	Moderate	GCS, IPC, LDUFH or LMWH
3–4	20–40%	High	IPC, LDUFH or LMWH
5	40–80%	Highest	Pharmacological: LDUFH, LMWH,[a] warfarin,[a] or Factor Xa inhibitor[a] alone or combined with GCS/IPC

[a] For use in patients undergoing hip or knee arthroplasty or hip fracture repair.
Source: Adapted from Ref. 126.



Thrombosis Risk Factor Assessment

Patient's Name:_____ Age: ____ Sex: ____ Wgt:____lbs

EVANSTON NORTHWESTERN HEALTHCARE

Joseph A. Caprini, MD, MS, FACS, RVT
Louis W. Bagley Professor of Surgery, Northwestern University
The Feinberg School of Medicine
Professor of Biomedical Engineering, Northwestern University
Director of Surgical Research, Evanston Northwestern Healthcare
Email: j-caprini@northwestern.edu
Website: venousdisease.com

Choose All That Apply

Each Risk Factor Represents 1 Point
- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (< 1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > 25)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Other risk factors_____

Each Risk Factor Represents 2 Points
- ❑ Age 60-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (> 45 minutes)
- ❑ Laparoscopic surgery (> 45 minutes)
- ❑ Patient confined to bed (> 72 hours)
- ❑ Immobilizing plaster cast (< 1 month)
- ❑ Central venous access

Each Risk Factor Represents 3 Points
- ❑ Age over 75 years
- ❑ History of DVT/PE
- ❑ **Family history of thrombosis***
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive Lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other congenital or acquired thrombophilia

If yes:
Type_____
*most frequently missed risk factor

Each Risk Factor Represents 5 Points
- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)

For Women Only (Each Represents 1 Point)
- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

Prophylaxis Safety Considerations: Check box if answer is 'YES'

Anticoagulants: Factors Associated with Increased Bleeding
- ❑ Is patient experiencing any active bleeding?
- ❑ Does patient have (or has had history of) heparin-induced thrombocytopenia?
- ❑ Is patient's platelet count <100,000/mm^3?
- ❑ Is patient taking oral anticoagulants, platelet inhibitors (e.g. NSAIDS, Clopidigrel, Salicylates)?
- ❑ Is patient's creatinine clearance abnormal? If yes, please indicate value _____

If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and should consider alternative prophylactic measures.

Intermittent Pneumatic Compression (IPC)
- ❑ Does patient have severe peripheral arterial disease?
- ❑ Does patient have congestive heart failure?
- ❑ Does patient have an acute superficial/deep vein thrombosis?

If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and should consider alternative prophylactic measures.

of this form allows one to go beyond the Guidelines since randomized, prospective data and appropriate clinical trials are not available for every circumstance the clinician sees in daily practice. As a result of this problem, one must take the available literature, incorporate the results of individual clinical trials when available, and assess an individual patient's risk for VTE to reach a tentative conclusion regarding the degree of thrombosis risk. In addition, one must apply a certain amount of logic, emotion, and experience to the overall clinical scenario in order to develop the best approach for each individual patient. This method is very conservative and has two dominant characteristics; namely, almost everyone gets prophylaxis, and the choice for each patient represents the best balance between efficacy and safety. We were a bit disappointed with the Consensus Guidelines when the statement was made that in orthopedic situations, the emphasis was on prevention of bleeding more than the prevention of thrombosis. Some of us would have a different view. Depending on the overall degree of risk of the patient, the selection of prophylaxis and intensity may carry more risk for bleeding; however, the intention is to prevent a fatal pulmonary embolus or disabling stroke. In today's world we feel that the patient should be a part of this discussion and decision-making process.

The most common pitfall we see in assessing risk in clinical practice is failure of the clinician to inquire about a past history of thrombosis or a family history of thrombosis. Some feel that the family history of thrombosis is not that important; however, we differ with this view based on results from our thrombosis referral clinic. We conducted a study where markers of probability were obtained in approximately 175 patients over a three-year period. Individuals who had a history of DVT were found to have a marker of thrombophilia 56% of the time. Those with a family history of thrombosis were found to have at least one abnormality at least 42% of the time. These defects included factor V Leiden, prothrombin 20210A, protein C and S, antithrombin deficiency, and antiphospholipid antibodies. We have seen examples of serious or fatal outcomes in our clinical practice when this history is not obtained and investigated thoroughly. We are always careful to assess the obstetrical history of every female in order to determine if a past stillborn infant, toxemia, recurrent spontaneous abortions, or placental insufficiency has occurred. These events may be clinical manifestations of the antiphospholipid antibody syndrome, including a lupus anticoagulant, which are severe risk factors for the development of postoperative VTE. We also investigate personal and family history of stroke and assess homocysteine levels. We believe that elevated levels should be treated with preventive doses of vitamin B6, B12 and folic acid in order to minimize the chance of endothelial damage from the elevated homocysteine levels that may produce a stroke, DVT or myocardial infarction. We realize that conflicting data exist in the literature regarding this principle (26), but until we see data that show there is some harm to this approach, we prefer to prescribe this therapy (27).

An example of our approach to risk assessment is our use of thrombosis prophylaxis in laparoscopic surgical patients, since this approach is not solely procedure-dependent but also based on the individual risk factors involved. Some investigators have reported that laparoscopic cholecystectomy is a low-risk procedure not requiring thrombosis prophylaxis (28). One study in 700 patients showed a VTE incidence of 1%. On further examination, the patients in this study all had fewer than three risk factors (29). We caution clinicians about translating these studies into routine clinical practice without first considering whether the individual patient might have a very high risk of developing a VTE. Patients undergoing laparoscopic surgery are like any other surgical patient in that the incidence of DVT is directly related to the risk factor score. This fact is well documented in the Chest Consensus Guidelines, as is seen in Table 3. The presence of pneumoperitoneum as well as reverse Trendelenburg position introduces additional

Table 5 Recommended Duration of VTE Prophylaxis for Various Indications

Indication	Duration of prophylaxis
Abdominal surgery	7–10 days [ref. (6)]
Abdominal surgery involving cancer	29 days [ref. (32)]
Hip fracture repair	4 wk [ref. (93)]
Hip arthroplasty	4–6 wk [ref. (30,31,63,87,88)]
Knee arthroplasty	10–14 days [ref. (89)]
Bariatric surgery	3 wk [ref. (125)]
Medical prophylaxis	10–14 days [ref. (11)]

elements of risk. These include decreased venous return resulting in venous stasis and venous dilatation that can produce endothelial cracks that serve as the nidus for development of postoperative venous thrombosis. Take, for example, the patient with acute cholecystitis, over the age of 60, with obesity, and a past history of successful treatment for cancer. We would classify this individual in the highest risk group (Table 4) with a score of eight to nine points. We would provide this patient with stockings and intermittent pneumatic compression devices during and following surgery, and low molecular weight heparin (LMWH) postoperatively for 10 to 30 days.

The duration of prophylaxis after surgery or hospitalization is important as well. It has been demonstrated that DVT prophylaxis should be continued for the duration the patient is at risk (30–33). These studies demonstrate that different durations of prophylaxis are appropriate for specific patients as shown in Table 5. When patients demonstrate several to many risk factors, it seems logical that multiple methods of DVT prevention may be used to further decrease the patient's risk (8). Considering all of these factors, our risk assessment schema accounts for many sources of risk (patient history, duration of protection needed, known prior VTE events, and clinical events not always recognized as related to VTE) not just the procedure itself. Only in this fashion may a selection for the appropriate prophylaxis be made that will fully protect the patient.

Physical Methods of Prophylaxis

Physical methods of prophylaxis may be divided into several categories, including graduated compression stockings (GCS), intermittent pneumatic compression devices (IPC), foot pumps, and combinations of foot and leg compression devices. GCS are stockings that have a higher pressure at the ankle than in the calf or thigh in order to provide a pressure profile that encourages blood flow out of the leg. The average pressure at the ankle is approximately 18 mmHg, which gradually decreases to approximately 8 mmHg in the thigh. These devices have been shown to decrease venous diameter slightly, which helps prevent venous distention, particularly when the limb is in the dependent position (34). Data to show the effectiveness of GCS appeared many years ago when it was legitimate to have a placebo group in thrombosis prophylaxis trials (20,35,36). Compared to doing nothing, these stockings improved results and lowered the incidence of venous thromboembolism. A summary of these results may be found in the 2000 Cochran analysis, which analyzed the results of a number of randomized clinical trials showing that the placebo incidence of DVT was 27% and was reduced to 13% utilizing GCS (37). Of even greater importance was the fact that when GCS was combined with another physical or pharmacologic method, the incidence of DVT was reduced from 15% using stockings alone to 2% in the combined modality group.

The IPC devices have been compared to placebo in 11 general surgery studies and demonstrated an impressive 74% reduction in DVT from 26% to 6.8% (8). We were disappointed that the Seventh Chest Consensus Guidelines contain very little discussion regarding these modalities and the editors do not clearly delineate between the differences in trials using stockings versus pneumatic compression devices. If one looks at the International Consensus statement published in 2001, it summarizes a number of landmark trials which show the effectiveness of IPC and differentiates them from graduated elastic compression stockings (8). In general, IPCs are more effective, but GCS remain useful. One real advantage of stockings is that they provide some protection when the patient is sitting in a chair. The pneumatic devices are normally disconnected when a patient is placed in a chair and, if no other form of prophylaxis is being used, the stockings become an important modality. Some clinicians would comment that moving surgical patients into a chair in the early postoperative period does not represent early *ambulation* but rather early *angulation*. Stockings also have a role when the patient is being transported for tests and, due to shortages in personnel, pneumatic devices may not be reconnected in a timely fashion when the patient returns to bed. Additionally, pneumatic devices may feel uncomfortable to the patient as perspiration collects next to the skin. The obstructive qualities of stockings underneath these devices may increase patient comfort and compliance. We feel that it is important for the reader to understand that IPC's are clearly different from GCS and that there are a number of advantages to using the combination of both modalities for greatest patient comfort and effectiveness.

Many investigators feel that although IPC's are effective, it is very difficult to obtain a high degree of patient compliance. This view has been expressed by Comerota who reported approximately a 35% compliance rate utilizing the devices in a university setting (38). We have employed IPC's in our hospitals for over 30 years with great success and have developed techniques to maximize compliance. Our technique involves both patient and nursing staff education. By utilizing these methods, we achieved an 85% compliance rate in a recent study involving total knee replacement patients (121). Q4 Teaching the patient that these devices are important to prevent blood clots and should be on at all times when they are not ambulating is the most important factor in our successful program.

The question of which device within each group (long or short GCS, or various IPC methods) is superior to another cannot be answered due to lack of appropriate randomized head-to-head trials. One recent study examined the added benefit of GCS compared to IPC when applied to patients receiving prophylaxis with low molecular weight heparin (LMWH) after arthroplasty. The authors discovered that the IPC group had 0% VTE rate compared to the 28.6% rate in the GCS group (39). This trial demonstrates further that a combination of modalities can improve the effectiveness of VTE prophylaxis.

In our opinion, there are three main indications for the use of the physical devices, the most obvious being in those patients where anticoagulants are contraindicated. Examples would be patients with active bleeding, patients with bleeding tumors or hematologic defects, and in operations upon the central nervous system including both neoplasms and vascular malformations (Table 6). The second very strong indication for T6 use of these physical methods is in the highest risk patients where the clinician attempts to reduce the incidence of VTE as much as possible. The study by Ramos involving 2551 patients undergoing cardiac surgery over a 10-years period is a good example of the value of combining anticoagulants and physical modalities to lower the incidence of PE (40). This trial represents the single best large example of how pneumatic devices can prevent pulmonary emboli and are more effective when combined with unfractionated heparin (UFH) than the use of unfractionated heparin alone. Another study by Kamran, although

Table 6 Many Uses for Pneumatic Compression

Hemostatic defects—hemophilia, Von Willebrand's disease, platelet functional defects, heparin-induced thrombocytopenia, etc.	History of venous thromboembolism, use in combination with pharmacologic prophylaxis
Post-cardiopulmonary bypass (CABG) procedures (along with heparin or LMWH)	Ruptured vessels—bleeding ulcers, bleeding from colitis or ileitis
Pelvic hematomas, and/or other complex trauma situations	Craniotomy or spinal cord surgery
Complex cancer operations—pancreatoduodenectomy, major hepatic resection, extensive pelvic resection, etc.[a]	Patients with stroke in the acute phase, and in combination with heparin or LMWH later, particularly those who cannot ambulate
In selected THR replacement patients at lower risk	All total knee replacements along with LMWH
Low risk of VTE, avoids anticoagulant bleeding[b]	

[a] Use alone until it is safe to start anticoagulants.
[b] In patients with only 2 risk factors.

not a randomized prospective study, clearly shows the benefits of adding pneumatic compression stockings and UFH for the prevention of DVT in stroke patients (41). The third indication for the use of physical methods is in patients with two risk factors where the incidence of DVT is 10–20% (see Table 3). The use of anticoagulants has never been shown to be better than using GCS and IPC combined for the prevention of venous thrombosis in this low-risk group of patients. Finally, as one who has used these devices for many years, I re-emphasize that, when using physical methods, combining IPC and GCS produces the best results. This opinion is based on 29 years of experience with IPC, observing many occasions during hospitalization where IPC devices were removed and their reapplication was delayed because of nursing personnel shortages (e.g., sending patients for diagnostic tests, getting them up in a reclining chair or to ambulate, wash or go to the bathroom). If the patient has GCS on, at least some degree of protection from venous stasis and overdistention of the venous system in the legs is afforded (34). If the patient cannot receive anticoagulants, we feel that the use of GCS alone is inadequate and will produce higher rates of venous thrombosis.

Unfractionated Heparin

The use of this drug for thrombosis prophylaxis in surgical patients can be traced to the pioneering work of Kakkar who, in 1977, reported a trial involving 28 hospitals and 4000 patients comparing small doses of UFH to placebo given to surgical patients postoperatively (42). The study clearly showed that UFH statistically significantly prevents all DVT compared to placebo and the incidence of fatal PE was reduced by 50% in the treated group (42). Table 7 shows these data, as well as the remarkable finding by Collins in 1988. He conducted a meta-analysis of all the trials that could be compared to the original Kakkar trial. This involved another 70 centers and 16,000 patients over a 15-years period. The results were exactly the same as the original trial (43). Once these data were available, the knowledge that UFH could lower the morbidity and mortality from thromboembolic disease after surgical procedures was unquestioned. For the next decade this drug became the standard for prevention of venous thromboembolism in these

Table 7 Early Use of Unfractionated Heparin for the Prevention of VTE in Surgical Patients

	Kakkar 1975 4000 pts, 28 centers		Collins 1988 16,000 pts, 70 centers	
Group	Control	Heparin	Control	Heparin
DVT	29.6%	9.40%	27.4%	10.6%
Fatal PE	1.7%	0.9%	3.4%	1.7%
Bleeding	5.80%	8.80%	1.80%	3.10%

surgical groups. As a matter of fact, UFH continues today to be the most widely used thrombosis prophylaxis modality in medical and surgical patients (44,45). This drug is very popular because it is inexpensive, has a half-life of under one hour, can be measured with the APTT, can be reversed easily with protamine, and is very familiar to generations of physicians.

The results of trials in general surgery involving UFH versus LMWH show varying results for thrombosis prophylaxis, with meta-analyses demonstrating either no difference between UFH and LMWH or improved VTE protection and lower bleeding complications with LMWH (46,47). One of the most recent trials by McLeod, a double-blind, randomized trial of 5000 units of UFH t.i.d. versus 40 mg QD of the LMWH enoxaparin, showed no significant differences in outcomes using UFH compared to LMWH in general surgical patients and the authors state that they prefer UFH due to its lower cost (48).

There are some disadvantages of unfractionated heparin, including the dreaded complication of heparin-induced thrombocytopenia (HIT). In susceptible patients heparin attaches to platelet Factor IV and stimulates an immune reaction which leads to platelet activation, clumping and thrombus formation. The syndrome usually develops after seven to ten days of heparin therapy and can recur in patients previously exposed to heparin (49,50). In this scenario the patient develops paradoxical clotting, most commonly manifested clinically as thrombotic episodes. At times, severe, disabling and often life-threatening strokes, pulmonary emboli, or thrombosis of the major arteries that are limb-threatening can result from HIT. This complication occurs in approximately 1% of patients receiving prophylactic or therapeutic doses of heparin (51). If one accounts for the cost of these complications, the economic advantage of UFH over LMWH is not so great (122). In addition, UFH inhibits platelet function to a greater degree than LMWH, which may produce more bleeding (46). Although both of these drugs are highly effective in general surgical patients, often neither one of them is used for fear of bleeding. Patients undergoing general, vascular, urologic, gynecologic and thoracic surgical procedures are often protected against thrombosis with stockings and/or IPC. Unfortunately, these modalities alone are only good for lower-risk surgical patients and not nearly as effective when patients have additional risk factors. In a study in our university academic setting, 70% of patients who were at very high risk did not receive appropriate thrombosis prophylaxis according to Consensus Conference Guidelines. The most commonly used form of prophylaxis in these individuals was a combination of stockings and pneumatic compression devices (123). Although long-term outcomes were not done as a part of this study, overall, patients on the surgical services had a higher than expected incidence of venous thrombosis compared to other hospitals (124). These data further illustrate that detailed individual risk assessment coupled with adherence to guidelines based on the risk factor point total is the key to reducing the incidence of thrombosis to the lowest possible level.

The under-use of thrombosis prophylaxis is not limited to surgical patients. One of the greatest needs in the medical community is to use appropriate thrombosis prophylaxis

in patients at risk according to Consensus Conference Guidelines. Three large clinical trials which were randomized and prospective clearly showed that 10 to 15% of medical patients admitted to hospital with additional risk factors can be expected to develop venous thrombosis without appropriate prophylaxis (53,54). These three trials were done with newer anti-thrombotic agents and the results will be described in subsequent sections of the text.

A common practice on both medical and surgical services is to administer UFH 5000 units b.i.d. as primary thrombosis prophylaxis. Bergmann, in a study of geriatric patients, showed that UFH 5000 units b.i.d. and 20 mg of enoxaparin were equivalent in preventing venous thrombosis (55). This dose of enoxaparin was subsequently found to be ineffective in reducing DVT in high-risk medical patients (11). There is good evidence in both the medical and surgical literature, however, that the use of 5000 units of UFH t.i.d. is superior to the b.i.d. dosing schedule (48,56). In fact, there is no large, randomized, prospective trial that shows the value of UFH 5000 units b.i.d. in medical patients. Three randomized, prospective trials in high-risk medical patients showed no differences between the b.i.d. heparin dosing and placebo (57–59). Goldhaber has commented on this problem, stating that "new onset VTE is more often caused by prophylaxis failure than lack of prophylaxis use" (60). In his series, patients readmitted to hospital with recurrent DVT most often had been given GCS or UFH b.i.d. alone as prophylactic modalities during the previous hospitalization. Many of these patients had multiple risk factors, with 80% having more than two risk factors. The majority of these patients were on medical services, not surgical services (where it is common for GCS, IPC and pharmacologic prophylaxis to be used together). These data indicate that GCS or UFH b.i.d. should not be used alone in patients at high risk for VTE.

Low Molecular Weight Heparin

This class of drugs was developed in the 1970s by chemical or enzymatic degradation of unfractionated heparin. In an attempt to isolate the part of the heparin molecule responsible for anticoagulant properties, a 19-saccharide chain was isolated from the original 50 saccharide units in unfractionated heparin. Low Molecular Weight Heparin (LMWH) solves many of the problems associated with UFH. Table 8 compares some of T8
the more important characteristics of both compounds. The improved bio-availability, longer half-life and freedom from routine monitoring were important characteristics, along with the lower incidence of HIT and heparin-induced osteoporosis. The most fascinating property of this class of drugs is the improved patient survival seen in cancer patients in studies comparing UFH and LMWH in patients with venous thromboembolism.

Dr. David Bergqvist from Uppsala, Sweden pioneered the use of low molecular weight heparin for thrombosis prophylaxis in surgical patients. His original observations found that LMWH had less influence on primary hemostasis than UFH in the animal model (61). Unfortunately, this initially led to too high dosing in early clinical prophylaxis studies. He performed the first pharmacokinetic and pharmacodynamic studies on LMWH, as well as extensive clinical studies using this drug in a variety of clinical scenarios over the next 20 years (28,62–68). He was also first to show the long-term benefits of LMWH for extended prophylaxis (69). Bergqvist also showed that larger prophylactic doses of LMWH were more effective than smaller prophylactic doses both in cancer and benign disease (70). He also demonstrated equal efficacy of several low molecular weight heparins compared to UFH in general surgical patients (62). One of his most important contributions was the recently completed Enoxacan II trial, which showed that 30 days of LMWH statistically significantly lowers the venographic incidence of venous thrombosis

Table 8 Advantages of LMWH Compared to UFH

UFH	LMWH
Nonspecific binding to plasma proteins, endothelial cells, and macrophages	More specific binding to ATIII
Variable anticoagulant effect, requires anticoagulant monitoring high-risk patients	Consistent and predictable anticoagulant effect
Monitoring required for high-risk patients	No anticoagulant monitoring required
Dosed q8h in high-risk patients	Most situations once daily dosing
Relatively poor bioavailability, especially low dose	Better bioavailability at low doses
Heparin resistance may occur	No heparin resistance
Short half-life	Longer half-life
	Redudced incidence of HIT and heparin-indudced osteoporosis
	Improved patient survival in patients with cancer

compared to seven days of LMWH prophylaxis. This study was done in abdominal surgery patients undergoing operations for cancer. For many of us who believe in extended outpatient prophylaxis, this study provided some guidelines as to the appropriate length of prophylaxis (63). However, if after 30 days the patient is still not ambulatory, then continued prophylaxis may be necessary because of the patient's continued VTE risk from immobilization, usually in a reclining chair.

Another fascinating property of LMWH was discovered in thrombosis treatment trials in patients with cancer who were randomized to receive either LMWH or UFH as initial treatment for their venous thrombosis. The patients in the LMWH group had a longer survival than did their counterparts who received UFH. This is a very complex association which is not well understood and has also been seen in some prophylaxis trials, most notably the work of Von Tempelhof (71). This trial involved the administration of only seven days of LMWH or UFH for prophylaxis following gynecologic oncology debulking pelvic procedures. 2400 days later, patients who had received LMWH only at the time of their surgery (seven days) had a statistically significantly better survival compared to their counterparts in the UFH group. Subsequent studies in cancer patients suggest that the administration of LMWH for one year in good-prognosis cancer patients without DVT prolonged their survival compared to those not receiving the drug (72,73). Additionally, other researchers have postulated that warfarin is not as effective as LMWH in cancer VTE prevention (74–76). While further studies are necessary to determine the effects on tumor biology, the authors would urge clinicians to prescribe LMWH whenever possible for prophylaxis or treatment of venous thromboembolic disease in patients with cancer, based on these studies.

Patients who present with multiple trauma suffer from a high incidence of VTE, which is seen over 70% of the time when long bone fractures are part of the clinical picture (77). Data have emerged to suggest that the administration of LMWH as prophylaxis in these trauma patients statistically significantly lowers the incidence of VTE compared to UFH prophylaxis (78). It is not always possible to employ anticoagulants in some of these patients, particularly those with closed head injury, pelvic fractures, or when lacerations of the liver or spleen are observed. Depending upon the risk of the patient, it is

sometimes necessary to introduce prophylactic vena cava filters, especially when the patient has a strong past history of venous thromboembolism, multiple markers of thrombophilia, the post-thrombotic syndrome, or severe chronic venous insufficiency. Duplex scan screening of these individuals has also been used as a strategy, but the sensitivity and specificity of this noninvasive modality in patients without symptoms of deep vein thrombosis varies widely among institutions (79,80).

A great many studies have been carried out in the orthopedic population using LMWH, particularly following total joint replacement. It has been nearly 20 years since the first trials employing LMWH compared to UFH following total hip replacement showed a statistically significant superiority in favor of LMWH (81,82). Initially this drug was administered close to the time of surgery or in the early postoperative period, which resulted in excessive bleeding (83,84). Subsequent studies have demonstrated that the administration of enoxaparin at 12 hr, or later postoperatively, is associated with a less than 0.5% incidence of bleeding. That percentage rises to 5.3% if the drug is administered eight hours postoperatively (85). The question of pre- or postoperative initiation of LMWH has not been completely settled. The European community tends to use a preoperative dose given 12 hours prior to surgery, while North American clinicians favor starting the drug 12 to 24 hours postoperatively. One recent trial involved the use of dalteparin given in two regimes which were prospectively randomized and analyzed with respect to both efficacy and bleeding risk (86). In one limb of the study, the drug was administered 12 hours preoperatively, given in a reduced dose 6 hours postoperatively, and then a full dose every 24 hours thereafter for a total of seven to 10 days. In the other limb of the study, the preoperative dose was omitted. The results showed that the efficacy of postoperative dosing compared to pre- and postoperative dosing was not statistically different, while those patients who received LMWH preoperatively suffered a higher incidence of bleeding complications. For many North American clinicians, this settled the question, although many of us recognize that further research needs to be completed.

Should LMWH prophylaxis be continued following discharge in total hip replacement patients? Bergqvist first demonstrated a 54% risk reduction with 30 days of LMWH prophylaxis compared to seven to 10 days postoperatively (30). A number of other authors subsequently confirmed these findings in this high-risk orthopedic population (31,63,87,88). The clinical and venographic incidence of VTE is statistically reduced following this extended prophylaxis in hip replacement surgery, hip fracture surgery, and in cancer patients who have endured surgery.

LMWH is also widely used following total knee replacement and is usually administered for seven to 10 days (89). Extended prophylaxis in this group of patients has not been shown to be necessary in prospective clinical trials (31). It has been our personal observation that many times these patients will be relatively immobile for four to six weeks following surgery, spending long periods of time in the recliner. These patients may require continued prophylaxis until they are fully ambulatory.

In the United States the use of oral anticoagulants following total joint replacement has been popular and approximately half of all patients are treated in this fashion. Many clinicians favor this approach because bleeding problems are minimal and the clinical incidence of VTE appears low. While prospective, randomized clinical trials such as the one by Hull showed venographic superiority in the prevention of VTE using LMWH compared to oral anticoagulants, warfarin still remains popular among clinicians (86,90). One reason for using the oral approach can be traced to the work of Colwell. This trial collected data from 156 centers and involved 3000 patients who were followed for 90 days following total hip replacement and randomly assigned to warfarin or enoxaparin. There was no statistically significant difference in the incidence of symptomatic VTE at

90 days between the two groups (91). LMWH enthusiasts would be quick to point out that there was a statistically significantly higher incidence of clinical VTE during hospitalization in the patients receiving oral anticoagulants. Only 1.1% of the patients had VTE and this was reduced to 0.3% in the LMWH group. Most clinicians did not consider this tiny reduction in incidence to be worth the potential increased bleeding and cost of LMWH. Additionally, both agents were given for 10–14 days, which is a shorter duration than what is recommended today. Some of us feel that looking only at a clinical endpoint is a very one-dimensional philosophy that does not address the overall advantages of LMWH to statistically significantly reduce the overall incidence of VTE. We are bothered by those who do not pay attention to venographic endpoints, arguing that they are artificial laboratory results that have little clinical significance. Kakkar demonstrated decades ago that delayed diagnosis of a clot led to damaged venous valves and to PTS (42). It would follow that inadequate prevention leads to asymptomatic clots that may not cause PE early in the course, but would lead to PTS and recurrent thrombosis. To those individuals, we point out that there are now several trials that demonstrate that venographic endpoints are surrogate markers for clinical events (92,93). We feel that in patients at extremely high risk for VTE, the use of a drug that provides the best efficacy should be selected.

LMWH prophylaxis has been used in medically ill patients in a number of studies, including the Medenox trial, which compared placebo, enoxaparin 20 mg/day, and enoxaparin 40 mg/day, in medical patients with one additional risk factor such as infection, heart failure, or pulmonary disease (11). The higher enoxaparin dose produced statistically significant improvement in the incidence of all VTE from 14.9% in the placebo group to 5.5% in the treated group. Interestingly, the lower-dose enoxaparin group had a 15% incidence of VTE compared to 14.9% in the placebo group. This study clearly illustrated that one must use not only the right drug, but also the right dose for a specific thrombosis prophylaxis indication. A second trial called the PREVENT trial involved dalteparin 5000 units a day in 3706 medically ill patients and showed a statistically significant reduction in the incidence of VTE from 4.96% to 2.77% (12).

The question of cost-effectiveness was first addressed by Bergqvist when he showed how patients who self-administered LMWH avoided clinical DVT (94,95). A number of other authors have studied the cost-effectiveness of using LMWH compared to UFH in both prophylactic and therapeutic studies. They conclude that the higher initial cost of the LMWH compared to UFH is justified because of the savings attributed to improved efficacy and reduced side-effects, particularly the dreaded HIT (96–99).

Fondaparinux

As the first synthetic Factor Xa inhibitor, fondaparinux further refines the quest for a specific inhibitor of clotting. Even with their successful use, LMWH still have limitations: b.i.d. dosing with many indications, cannot be used in HIT, and they are derived from animal sources. Many years of research during the 1980s led to the realization that only a 5-sugar sequence was required for antithrombotic activity. In collaboration, the Institute of Choay, Sanofi-Synthelabo, and Organon synthesized a 5-sugar molecule, fondapairnux, which would bind to antithrombin 94% and increase antithrombin affinity for Factor Xa by 300-fold (100–102). The specific binding and small size of fondaparinux also results in a lack of cross-reactivity with platelet Factor IV, resulting in a substantially reduced ability to promote HIT (50,103). Early research demonstrated its effectiveness in prevention of DVT in hip and knee replacement with a fixed, once-daily subcutaneous injection (104).

A large study program in hip replacement, knee replacement, and hip fracture repair introduced fondaparinux to orthopedic care. Fondaparinux was compared to both the European and North American conventional doses of enoxaparin in a randomized, double-blind fashion. Fondaparinux reduced the occurrence of venographically detected venous thrombosis over 50% better than did enoxaparin (105). Patients undergoing knee replacement experienced a higher bleeding rate in the fondaparinux group (106). An analysis of the timing of dosage initiation demonstrated that excess bleeding risk was attributable to drug administration less than four hours after surgery, similar to the LMWH trial by Hull (86). The researchers found that the preferred administration time for fondaparinux came six to eight hours after surgery (105,107). Subsequently it was found that next-day (<24 hr) administration maintained efficacy but reduced bleeding in patients following total hip or knee replacement (108). Pharmacoeconomic studies have demonstrated that fondaparinux is more cost-effective when chosen instead of enoxaparin in several models in the United States and Europe (109–113).

With regard to extended prophylaxis in orthopedic surgery, Eriksson pursued the ability of fondaparinux to reduce VTE events in patients undergoing hip fracture repair. Compared to seven days of prophylaxis, 30 days of fondaparinux prophylaxis reduced the event rate from 35% to 1.4%. Additionally, the symptomatic event rate was significantly reduced from 2.7% to 0.3%, nearly eliminating VTE (93). This trial is a significant contribution to patient care. First, it confirmed the ability of a venogram to accurately predict the effects on clinical VTE events; both were prevented by 90%. Second, unlike previous studies, this study was able to identify beneficial effects on symptomatic events alone in only 656 patients, confirming the benefit of fondaparinux prophylaxis. Additionally, with four weeks of fondaparinux treatment, major bleeding was no different from placebo.

With its success in DVT prevention after orthopedic surgery, fondaparinux was studied in other indications as well. Abdominal surgery patients at risk for postoperative DVT were assigned to fondaparinux or a pre-op/post-op dosage of dalteparin in a double-blind fashion. Both drugs reduced the VTE rate similarly; however, unexpectedly, fondaparinux reduced the VTE rate in the cancer cohort significantly compared to dalteparin. Major bleeding was low for both agents (114). This is the first study comparing fondaparinux to LMWH in a cancer cohort. These interesting results await larger, more specific trials in cancer patients receiving surgical treatment as well as DVT prevention in patients being medically treated for cancer.

A European placebo-controlled trial was undertaken to determine the effect of fondaparinux in the prevention of VTE in patients hospitalized for medical illness. This was possible due to the low rate of heparin or LMWH utilization in medical patients at the time the trial was conducted. Fondaparinux significantly reduced the VTE rate in medical patients compared to placebo from 10.5% to 5.6%, with no significant difference in major bleeding. Additionally, fondaparinux reduced the rate of death due to PE from 1.5% to 0% (53). This was the first time a single study demonstrated reduced mortality in medical prophylaxis patients. Previous meta-analysis of many LMWH demonstrated reduced mortality in medical and cancer patients receiving prophylaxis as described earlier.

Fondaparinux is undergoing evaluation by the FDA for prophylaxis after abdominal surgery and in medical prophylaxis. Its place in therapy has been addressed for its current indications in orthopedics by the Consensus Conference Guidelines. It has been given FDA approval in hip fracture patients for both standard and extended prophylaxis, is a useful prophylactic agent in high-risk patients, and can prevent VTE better than LMWH. Proper administration time after surgery, and avoidance in patients with severe renal

dysfunction (creatinine clearance <30 ml/min), will optimize its safety. This agent demonstrates again that patient-specific risk assessment is needed in order to enjoy the benefits and minimize the risk of thrombosis prophylaxis.

Ximelagatran

For many years warfarin was the only oral anticoagulant available for long-term thrombosis prophylaxis in patients with chronic atrial fibrillation and mechanical heart valves, and as primary treatment after an initial period of heparin therapy in patients with VTE. Warfarin has also been the mainstay of long-term prophylaxis in VTE. It has been widely used as primary thrombosis prophylaxis after major orthopedic surgery, particularly in joint replacements and following hip fracture surgery. However, warfarin has a slow onset of action and is inconvenient because it requires frequent coagulation monitoring and dose adjustments. In addition, the anticoagulant properties of warfarin can be affected by certain foods, alcoholic beverages, and a wide variety of medications. The logistics of managing warfarin may be cumbersome in certain clinical situations, particularly in those individuals who do not have access to coagulation clinics or other advanced health-care management systems that specialize in patient monitoring. A small subset of patients exists in whom maintaining appropriate levels of anticoagulation is a difficult chore due to warfarin resistance or other factors (115).

Over the past few years a new oral anticoagulant called ximelagatran has been developed. Taken orally, this drug undergoes a rapid biotransformation in the GI tract to melagatran. It directly inhibits thrombin, both clot-bound and circulating in plasma. Melagatran is not metabolized, and 80% of the drug is excreted renally. It is not bound to plasma proteins and has a low potential for food or drug interactions. This drug does not require routine anticoagulant monitoring; however, it does require liver enzyme tests (AST, ALT, bilirubin) monthly. Fixed dosing produces a predictable dose response and it must be taken twice daily. Melagatran reaches a peak concentration in the blood in two hours and has a four-to-five-hours half-life. It has a pharmacokinetic profile comparable to LMWH. This drug has undergone an extensive clinical trial program involving nearly 30,000 patients. The clinical areas involved in these studies include DVT prophylaxis after orthopedic surgery and in medically ill patients, DVT treatment both primary and extended prophylaxis, atrial fibrillation, and in patients with certain acute coronary syndromes (116–119). This clinical program has been very successful regarding efficacy endpoints; however, at the present time, concern over liver function test elevations has prevented this drug from achieving FDA approval in the United States (120). The drug has been approved for short-term use in a number of European countries and has been used in about 50,000 patients. To date, no serious liver-related problems have been observed.

KEY POINTS

- Venous thromboembolism (VTE) is a major cause of mortality particularly in the elderly, in those undergoing surgery and in those with cancer
- Longer term the post-thrombotic syndrome occurs in 25% of those with a DVT
- All patients should undergo a formal risk assessment for VTE
- Physical measures such as graduated compression stockings and intermittent pneumatic compression are effective
- Physical measures should be particularly considered in those where anticoagulants are contraindicated or where there is high risk

- Pharmacological prophylaxis includes unfractionated heparin and low-molecular weight heparin
- Newer agents including direct factor Xa inhibitors are being developed and introduced.

REFERENCES

1. Cushman M, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004; 117:19–25. Q6
2. National Center for Health Statistics Fast Facts Web site. www.cdc.gov/nchs/fastfacts/mamogram.htm. accessed Decmeber 15, 2004.
3. National Center for Health Statistics Report 2002; 53:1–116. www.cdc.gov/nchs/data/nvsr/nvsr53/nvsr53_05.pdf, accessed December 15, 2004.
4. Kniffin WD, Jr, et al. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. Arch Intern Med 1994; 154:861–866.
5. Anderson FA, Jr, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991; 151:933–938.
6. Geerts WH, et al. Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:338S–400S.
7. Bhattacharyya T, Iorio R, Healy WL. Rate of and risk factors for acute inpatient mortality after orthopaedic surgery. J Bone Joint Surg Am 2002; 84-A:562–572.
8. Nicolaides AN, et al. Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. Int Angiol 2001; 20:1–37.
9. Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA 1995; 274:335–337.
10. Fraisse F, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. Am J Respir Crit Care Med 2000; 161:1109–1114.
11. Samama MM, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med 1999; 341:793–800.
12. Leizorovicz A, Mismetti P. Preventing venous thromboembolism in medical patients. Circulation 2004; 110:IV13–IV19.
13. Kakkar AK, Williamson RC. Prevention of venous thromboembolism in cancer patients. Semin Thromb Hemost 1999; 25:239–243.
14. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988; 208:227–240.
15. Prandoni P, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996; 125:1–7.
16. Prandoni P, Lensing AW, Prins MR. The natural history of deep-vein thrombosis. Semin Thromb Hemost 1997; 23:185–188.
17. Prandoni P, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. Haematologica 1997; 82:423–428.
18. Siragusa S, et al. [Clinical course and incidence of post-thrombophlebitic syndrome after profound asymptomatic deep vein thrombosis. Results of a transverse epidemiologic study]. Minerva Cardioangiol 1997; 45:57–66.
19. Kahn SR. Venous thrombosis in long-haul travelers. Arch Intern Med 2004; 164:1699–1700 (author reply 1700).

20. Borow M, Goldson H. Postoperative venous thrombosis. Evaluation of five methods of treatment. Am J Surg 1981; 141:245–251.
21. Brandjes DP, ten Cate JW, Buller HR. Pre-surgical identification of the patient at risk for developing venous thromboembolism post-operatively. Acta Chir Scand Suppl 1990; 556:18–21.
22. Caprini JA, et al. Low molecular weight heparins and external pneumatic compression as options for venous thromboembolism prophylaxis: a surgeon's perspective. Semin Thromb Hemost 1991; 17:356–366.
23. Geerts WH, et al. Prevention of venous thromboembolism. Chest 2001; 119:132S–175S.
24. Clagett GP, et al. Prevention of venous thromboembolism. Chest 1998; 114:531S–560S.
25. Kessler CM. Propensity for hemorrhage and thrombosis in chronic myeloproliferative disorders. Semin Hematol 2004; 41:10–14.
26. Peeters AC, et al. The effect of homocysteine reduction by B-vitamin supplementation on markers of endothelial dysfunction. Thromb Haemost 2004; 92:1086–1091.
27. Stanger O, et al. Clinical use and rational management of homocysteine, folic acid, and B vitamins in cardiovascular and thrombotic diseases. Z Kardiol 2004; 93:439–453.
28. Bergqvist D, Lowe G. Venous thromboembolism in patients undergoing laparoscopic and arthroscopic surgery and in leg casts. Arch Intern Med 2002; 162:2173–2176.
29. Baca I, et al. [Prevention of thromboembolism in minimal invasive interventions and brief inpatient treatment. Results of a multicenter, prospective, randomized, controlled study with a low molecular weight heparin]. Chirurg 1997; 68:1275–1280.
30. Bergqvist D, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med 1996; 335:696–700.
31. Comp PC, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am 2001; 83-A:336–345.
32. ENOXACAN Study Group. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. Br J Surg 1997; 84:1099–1103.
33. Eriksson BI, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001; 345:1298–1304.
34. Arcelus JI, et al. Home use of impulse compression of the foot and compression stockings in the treatment of chronic venous insufficiency. J Vasc Surg 2001; 34:805–811.
35. Turner GM, Cole SE, Brooks JH. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis after major gynaecological surgery. Br J Obstet Gynaecol 1984; 91:588–591.
36. Holford CP. Graded compression for preventing deep venous thrombosis. Br Med J 1976; 2:969–970.
37. Amarigiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev 2000; 3:CD001484.
38. Comerota AJ, Katz ML, White JV. Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? Am J Surg 1992; 164:265–268.
39. Silbersack Y, et al. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in combination with intermittent pneumatic compression. J Bone Joint Surg Br 2004; 86:809–812.
40. Ramos R, et al. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. Chest 1996; 109:82–85.
41. Kamran SI, Downey D, Ruff RL. Pneumatic sequential compression reduces the risk of deep vein thrombosis in stroke patients. Neurology 1998; 50:1683–1688.
42. Kakkar VV, et al. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. Lancet 1977; 1:567–569.
43. Collins R, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med 1988; 318:1162–1173.

44. Caprini JA, et al. The use of low molecular weight heparins for the prevention of postoperative venous thromboembolism in general surgery. A survey of practice in the United States. Int Angiol 2002; 21:78–85.
45. Caprini JA, et al. Prevention of venous thromboembolism in North America: results of a survey among general surgeons. J Vasc Surg 1994; 20:751–758.
46. Mismetti P, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001; 88:913–930.
47. Koch A, et al. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. Br J Surg 1997; 84:750–759.
48. McLeod RS, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the Canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Ann Surg 2001; 233:438–444.
49. Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. Semin Hematol 1998; 35:9–16 (discussion 35–36).
50. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:311S–337S.
51. Warkentin TE, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335.
52. Krotenberg R, et al. Dalteparin vs. enoxaparin as prophylaxis for deep-vein thrombosis after total hip or knee arthroplasty: a retrospective analysis. Am J Phys Med Rehabil 2001; 80:889–895.
53. Cohen AT, xxx GAS, Lassen MR, et al. Fondaparinux vs. placebo for the prevention of venous thromboembolism in acutely ill medical patients (artemis). J Thromb Haemost 2003; 1:P2046.
54. Turpie AG. Thrombosis prophylaxis in the acutely ill medical patient: insights from the prophylaxis in MEDical patients with ENOXaparin (MEDENOX) trial. Am J Cardiol 2000; 86:48M–52M.
55. Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. The Enoxaparin in Medicine Study Group. Thromb Haemost 1996; 76:529–534.
56. Kleber FX, et al. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J 2003; 145:614–621.
57. Gardlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. Lancet 1996; 347:1357–1361.
58. Cade JF, Andrews JT, Stubbs AE. Comparison of sodium and calcium heparin in prevention of venous thromboembolism. Aust N Z J Med 1982; 12:501–504.
59. Halkin H, et al. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. Ann Intern Med 1982; 96:561–565.
60. Goldhaber SZ, Dunn K, MacDougall RC. 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. Chest 2000; 118:1680–1684.
61. Holmer E, et al. Heparin and its low molecular weight derivatives: anticoagulant and antithrombotic properties. Haemostasis 1986; 16:1–7.
62. Bergqvist D. Prophylaxis of postoperative deep vein thrombosis in general surgery: experiences with fragmin. Acta Chir Scand Suppl 1988; 543:87–89.
63. Bergqvist D, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346:975–980.

64. Bergqvist D, et al. Thromboprophylactic effect of low molecular weight heparin started in the evening before elective general abdominal surgery: a comparison with low-dose heparin. Semin Thromb Hemost 1990; 16:19–24.
65. Bergqvist D, et al. Thromboprophylaxis with a low molecular weight heparin (tinzaparin) in emergency abdominal surgery. A double-blind multicenter trial. Vasa 1996; 25:156–160.
66. Bergqvist D, Lindblad B, Matzsch T. Low molecular weight heparin for thromboprophylaxis and epidural/spinal anaesthesia—is there a risk? Acta Anaesthesiol Scand 1992; 36:605–609.
67. Bergqvist D, et al. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888–891.
68. Bergqvist D, Nilsson B. The influence of low molecular weight heparin in combination with dihydroergotamine on experimental thrombosis and haemostasis. Thromb Haemost 1987; 58:893–895.
69. Bergqvist D. Prolonged prophylaxis against postoperative venous thromboembolism. Haemostasis 1996; 26:379–387.
70. Bergqvist D, et al. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 XaI units in 2070 patients. Br J Surg 1995; 82:496–501.
71. von Tempelhoff GF, et al. Effect of low molecular weight heparin (Certoparin) versus unfractionated heparin on cancer survival following breast and pelvic cancer surgery: A prospective randomized double-blind trial. Int J Oncol 2000; 16:815–824.
72. Kakkar AK, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). J Clin Oncol 2004; 22:1944–1948.
73. Altinbas M, et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. J Thromb Haemost 2004; 2:1266–1271.
74. Lee AY. Epidemiology and management of venous thromboembolism in patients with cancer. Thromb Res 2003; 110:167–172.
75. Lee AY. The role of low-molecular-weight heparins in the prevention and treatment of venous thromboembolism in cancer patients. Curr Opin Pulm Med 2003; 9:351–355.
76. Cosmi B, Palareti G. Oral anticoagulant therapy in venous thromboembolism. Semin Vasc Med 2003; 3:303–314.
77. Geerts WH, et al. A prospective study of venous thromboembolism after major trauma. N Engl J Med 1994; 331:1601–1606.
78. Geerts WH, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med 1996; 335:701–707.
79. Cipolle MD, et al. The role of surveillance duplex scanning in preventing venous thromboembolism in trauma patients. J Trauma 2002; 52:453–462.
80. Kadyan V, et al. Surveillance with duplex ultrasound in traumatic spinal cord injury on initial admission to rehabilitation. J Spinal Cord Med 2003; 26:231–235.
81. Planes A, et al. Enoxaparine low molecular weight heparin: its use in the prevention of deep venous thrombosis following total hip replacement. Haemostasis 1986; 16:152–158.
82. Turpie AG, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med 1986; 315:925–929.
83. Spiro TE, et al. Efficacy and safety of enoxaparin to prevent deep venous thrombosis after hip replacement surgery. Enoxaparin Clinical Trial Group. Ann Intern Med 1994; 121:81–89.
84. Colwell CW, Jr, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am 1994; 76:3–14.

85. Fitzgerald RH, Jr, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am 2001; 83-A:900–906.
86. Hull RD, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. Arch Intern Med 2000; 160:2199–2207.
87. Dahl OE, et al. Prolonged thromboprophylaxis following hip replacement surgery—results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). Thromb Haemost 1997; 77:26–31.
88. Dahl OE, Pleil AM. Investment in prolonged thromboprophylaxis with dalteparin improves clinical outcomes after hip replacement. J Thromb Haemost 2003; 1:896–906.
89. Leclerc JR, et al. Prevention of deep vein thrombosis after major knee surgery—a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. Thromb Haemost 1992; 67:417–423.
90. Hull RD, et al. Subcutaneous low-molecular-weight heparin vs warfarin for prophylaxis of deep vein thrombosis after hip or knee implantation. An economic perspective. Arch Intern Med 1997; 157:298–303.
91. Colwell CW, Jr, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three mo after discharge. J Bone Joint Surg Am 1999; 81:932–940.
92. Eriksson BI, et al. Influence of the duration of fondaparinux (Arixtra) prophylaxis in preventing venous thromboembolism following major orthopedic surgery. J Thromb Haemost 2003; 1:383–384.
93. Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med 2003; 163:1337–1342.
94. Bergqvist DT, Matzsch T. Cost/benefit aspects on thromboprophylaxis. Haemostasis 1993; 23:15–19.
95. Bergqvist D, Lindgren B, Matzsch T. Comparison of the cost of preventing postoperative deep vein thrombosis with either unfractionated or low molecular weight heparin. Br J Surg 1996; 83:1548–1552.
96. McGarry LJ, Thompson D. Retrospective database analysis of the prevention of venous thromboembolism with low-molecular-weight heparin in acutely III medical inpatients in community practice. Clin Ther 2004; 26:419–430.
97. de Lissovoy G, Subedi P. Economic evaluation of enoxaparin as prophylaxis against venous thromboembolism in seriously ill medical patients: a US perspective. Am J Manag Care 2002; 8:1082–1088.
98. Botteman MF, et al. Results of an economic model to assess the cost-effectiveness of enoxaparin, a low-molecular-weight heparin, versus warfarin for the prophylaxis of deep vein thrombosis and associated long-term complications in total hip replacement surgery in the United States. Clin Ther 2002; 24:1960–1986 (discussion 1938).
99. Nerurkar J, Wade WE, Martin BC. Cost/death averted with venous thromboembolism prophylaxis in patients undergoing total knee replacement or knee arthroplasty. Pharmacotherapy 2002; 22:990–1000.
100. Walenga JM, et al. The inhibition of the generation of thrombin and the antithrombotic effect of a pentasaccharide with sole anti-factor Xa activity. Thromb Res 1988; 51:23–33.
101. Petitou M, et al. Synthesis of heparin fragments. A chemical synthesis of the pentasaccharide O-(2-deoxy-2-sulfamido-6-O-sulfo-alpha-D-glucopyranosyl)-(1-4)-O-(beta-D-glucopyranosyluronic acid)-(1-4)-O-(2-deoxy-2-sulfamido-3,6-di-O-sulfo-alpha-D-glu copyranosyl)-(1-4)-O-(2-O-sulfo-alpha-L-idopyranosyluronic acid)-(1-4)-2-deoxy-2-sulfamido-6-O-sulfo-D-glucopyranose decasodium salt, a heparin fragment having high affinity for antithrombin III. Carbohydr Res 1986; 147:221–236.

102. Choay J, et al. Structure-activity relationship in heparin: a synthetic pentasaccharide with high affinity for antithrombin III and eliciting high anti-factor Xa activity. Biochem Biophys Res Commun 1983; 116:492–499.
103. Savi P, et al. Effect of fondaparinux on platelet activation in the presence of heparin-dependent antibodies. A blinded comparative multicenter study with unfractionated heparin. Blood 2004.
104. Turpie AG, Gallus AS, Hoek JA. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 2001; 344:619–625.
105. Turpie AG, et al. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002; 162:1833–1840.
106. Bauer KA, et al. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001; 345:1305–1310.
107. Bauer KA, et al. Factor Xa inhibition in the prevention of venous thromboembolism and treatment of patients with venous thromboembolism. Curr Opin Pulm Med 2002; 8:398–404.
108. Pineo GF, Hull RD. Dalteparin sodium. Expert Opin Pharmacother 2001; 2:1325–1337.
109. Sullivan SD, et al. A cost-effectiveness analysis of fondaparinux sodium compared with enoxaparin sodium as prophylaxis against venous thromboembolism: use in patients undergoing major orthopaedic surgery. Pharmacoeconomics 2004; 22:605–620.
110. Gordois A, et al. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. J Thromb Haemost 2003; 1:2167–2174.
111. Spruill WJ, Wade WE, Leslie RB. A cost analysis of fondaparinux versus enoxaparin in total knee arthroplasty. Am J Ther 2004; 11:3–8.
112. Spruill WJ, Wade WE, Leslie RB. Cost analysis of fondaparinux versus enoxaparin as venous thromboembolism prophylaxis in elective hip replacement surgery. Blood Coagul Fibrinolysis 2004; 15:539–543.
113. Dranitsaris G, et al. Pharmacoeconomic analysis of fondaparinux versus enoxaparin for the prevention of thromboembolic events in orthopedic surgery patients. Am J Cardiovasc Drugs 2004; 4:325–333.
114. Agnelli G, Bergqvist D, Cohen A, Gallus A, Gent M. A randomized double-blind study to compare the efficacy and safety of fondaparinux with dalteparin in the prevention of venous thromboembolism after high-risk abdominal surgery: the Pegasus study. J Thromb Haemost 2003; 1:OC006.
115. Hirsh J. Current anticoagulant therapy—unmet clinical needs. Thromb Res 2003; 109:S1–S8.
116. Colwell CW, Jr, et al. Comparison of ximelagatran, an oral direct thrombin inhibitor, with enoxaparin for the prevention of venous thromboembolism following total hip replacement. A randomized, double-blind study. J Thromb Haemost 2003; 1:2119–2130.
117. Eriksson BI. Clinical experience of melagatran/ximelagatran in major orthopaedic surgery. Thromb Res 2003; 109:S23–S29.
118. Schulman S, et al. Secondary prevention of venous thromboembolism with the oral direct thrombin inhibitor ximelagatran. N Engl J Med 2003; 349:1713–1721.
119. Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). Am Heart J 2003; 146:431–438.
120. FDA Cardiovascular and Renal Drugs Advisory Committee Board, September 10, 2004. http//www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4069b1.htm. accessed December 15, 2004.
121. Caprini JA, Oyslender M, Robb WJ. Thrombosis prophylaxis following total knee replacement. Poster presentation, American Venous Forum, San Diego, CA, February 9–13 2005.
122. Weinberg M, Lichtig LK, Caprini JA, Merli GL, Vogenberg FR. Implications of heparin utilization for medical at-risk patients. Submitted for publication. Q8

123. Caprini JA, Glase C, Martchev D, Oyslender M, Arcelus JI. Thrombosis risk factor assessment in surgical patients: compliance with chest consensus guidelines. Poster presentation, American Venous Forum, Cancun, Mexico, February 20–23, 2003.
124. Personal communication, Solucent database, 2004.
125. Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. Obes Surg 2000; 10:7–14.
126. Chest 2004, Nicolaides, Scope, Turpie meta-analysis, Ringley Am Surgeon 2002, Morris Arch Surg 2002.