

Chapter 12

The prophylaxis and treatment of venous thrombo-embolism

Joseph A. Caprini MD MS FACS RVT

*Louis W. Biegler Professor of Surgery and Bioengineering, Department of Surgery,
Evanston Northwestern Healthcare, Evanston, Illinois, USA*

*Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA and
Robert R. McCormick School of Engineering and Applied Sciences, Evanston, Illinois, USA*

Introduction

Venous thrombo-embolism (VTE), a serious disease that encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE), continues to be a significant cause of morbidity and mortality ^{1, 2}. As many as 145 individuals per 100,000 in the general population develop symptomatic DVT every year, and up to 69 individuals per 100,000 experience PE ³. One-year mortality rates can be up to 21% for DVT and more than 50% for PE ^{4, 5}. Long-term complications of DVT of the lower extremity, including proximal or distal calf vein thrombosis, include post-thrombotic syndrome (PTS), resulting from chronic venous insufficiency to the affected limb, and recurrent VTE ⁶. PTS is characterised by permanent vein damage, resulting in chronic leg swelling that worsens during the day and that may be accompanied by varicose veins, oedema, skin discoloration, and skin ulceration ^{6, 7}. PE can be classified as massive, which is often fatal and must be resolved immediately by thrombolysis, or non-massive, which is not immediately life-threatening and can be treated with anticoagulation. Long-term complications of PE include increased pulmonary artery pressure, pulmonary hypertension, and right-sided heart failure ⁸. These serious, disabling, and sometimes fatal consequences of VTE underscore the importance of prevention in patients at risk.

VTE risk assessment

Risk for VTE should be assessed in all hospitalised patients. This practice is endorsed by the National Quality Forum (NQF), which

published a consensus report on safe practices for better healthcare in 2003⁹. NQF-endorsed safe practice #17 states that physicians should "evaluate each patient upon admission, and regularly thereafter, for the risk of developing DVT/VTE. Utilise clinically appropriate methods to prevent DVT/VTE." Risk assessment is required to stratify patients, according to overall VTE risk, to allow for optimal decision making regarding VTE prophylaxis, including modality, agent, and duration of prophylaxis¹⁰. Risk assessment can also be a useful aid in the diagnosis of VTE and may be used to guide decisions about the duration of treatment following an acute episode of VTE¹⁰.

Risk factors

Because risk category placement is dependent on the presence of factors that influence the risk for VTE, identification of VTE risk factors is critical for the appropriate initiation of therapy¹. There is a wide range of hereditary, medical, and surgical conditions that may increase the risk for VTE (Table 1), and the presence of multiple risk factors can cumulatively increase the risk for a thrombo-embolic event^{11, 12}. Different patient populations have different risk for VTE. The prevalence of DVT without treatment is particularly high among patients who have undergone major orthopaedic surgery (40% to 84%) or who have experienced major trauma (30% to 70%) or a spinal cord injury (50% to 90%)¹³. The prevalence of VTE without treatment in general surgical patients is approximately 30%^{14, 15}. The prevalence of asymptomatic DVT without treatment in general medical patients ranges from 5% to 15%¹⁶⁻²². A complete patient history is necessary to identify factors in the clinical setting, patient factors, and thrombophilic factors that put a patient at risk for VTE.

Risk assessment models (RAMs) have been developed by assigning weight to VTE risk factors (based on the risk for VTE that they confer to a patient) to determine a patient's total risk factor score. This score can help guide physicians in prescribing an optimal VTE prophylaxis regimen for each patient.

Table 1 Inherited, acquired, medical, and surgical risk factors for VTE ²³⁻²⁸.**Hereditary and acquired risk factors**

- Lupus anticoagulant, anticardiolipin, and antiphospholipid antibodies
- Hyperhomocysteinaemia
- Dysfibrinogenaemia
- Myeloproliferative disorders
- Antithrombin deficiency
- Factor V Leiden (activated protein C resistance)
- Disseminated intravascular coagulation
- Polycythaemia vera
- Disorders of plasminogen and plasminogen activation
- Heparin-induced thrombocytopenia
- Protein C deficiency
- Protein S deficiency
- Hyperviscosity syndromes
- Prothrombin gene mutation 20210A
- Heparin cofactor II deficiency
- Primary thrombocytosis
- Elevated FVIII, IX, XI levels

Medical risk factors

- Age >40 years
- Prolonged immobility
- Prolonged confinement to bed or lower limb paralysis
- History of venous thrombo-embolism
- Cancer
- Myocardial infarction
- Stroke
- Cardiac dysfunction or congestive heart failure
- Acute respiratory failure
- Pregnancy
- Obesity
- Varicose veins
- Oestrogen use
- Inflammatory bowel disease
- Nephrotic syndrome
- Indwelling femoral vein catheter/central lines
- Pacemaker wires
- Sepsis
- Endothelial damage (of any cause)

Surgical risk factors

- Major surgery (especially involving the abdomen, pelvis or lower extremities)
- Trauma or fractures to the pelvis, hip, or lower extremities
- Total hip replacement
- Total knee replacement

Risk assessment models

Ideal risk assessment models should apply to all types of hospital patients and be quick and simple to use, based on factors easily identified from medical history and physical examination. Patients should be stratified according to overall risk level, and specific recommendations for appropriate thromboprophylaxis should be based on evidence from randomised controlled trials^{29, 30}. Several RAMs that meet these criteria have been published^{1, 29, 31}. Caprini and colleagues combined the strengths of available RAMs and drew on consensus documents to develop a simple, self-contained scoring system for risk stratification of both surgical and medical patients, based on clearly defined clinical settings and the presence of specified risk factors (Table 2)¹⁰. This RAM can be used to assign each patient a total risk factor score, which can then be used to categorise patients into one of four risk categories (low, moderate, high, and highest)¹⁰. An appropriate method of VTE prophylaxis can be chosen based on the level of risk, taking into consideration any contra-indications to prophylaxis.

Kucher, Goldhaber and colleagues evaluated a RAM linked to a computerised system that alerted the responsible physician to a patient's increased risk for VTE³². The programme used eight common risk factors (cancer, prior VTE, hypercoagulability, major surgery, advanced age, obesity, bed rest, and the use of hormone replacement therapy or oral contraceptives) to determine each hospitalised patient's risk for VTE. Patients at increased risk were randomised to the electronic alert group or a control group. Significantly ($p < 0.001$) more patients in the electronic alert group received mechanical or pharmacologic prophylaxis. At 90 days, 4.9% of patients in the electronic alert group experienced DVT or a PE compared with 8.2% of patients in the control group, a reduction of 41%. Goldhaber's results suggest that the use of RAMs to identify and treat patients at risk for VTE can significantly reduce the rate of VTE.

Selected highlights of VTE prophylaxis

2004 ACCP guidelines for VTE prophylaxis

Beginning in 1986 and at each three-year interval thereafter, the American College of Chest Physicians (ACCP) has published consensus

Table 2 Proposed VTE RAM for surgical and medical patients (adapted from Caprini *et al*¹⁰).**Step 1: Exposing risk factors associated with clinical setting**

Each risk factor represents 1 point	Each risk factor represents 2 points	Each risk factor represents 3 points	Each risk factor represents 5 points
<input type="checkbox"/> Minor surgery	<input type="checkbox"/> Major surgery* <input type="checkbox"/> Immobilizing plaster cast <input type="checkbox"/> Patients confined to bed >72 hours <input type="checkbox"/> Central venous access <input type="checkbox"/> Arthroscopic surgery	<input type="checkbox"/> Myocardial infarction <input type="checkbox"/> Congestive heart failure <input type="checkbox"/> Severe sepsis/ infection	<input type="checkbox"/> Elective major lower extremity arthroplasty <input type="checkbox"/> Hip, pelvis, or leg fracture (<1 month) <input type="checkbox"/> Stroke (<1 month) <input type="checkbox"/> Multiple trauma (<1 month) <input type="checkbox"/> Acute spinal cord injury (<1 month)

*Operations in which the dissection is important or that last longer than 45 minutes, including laparoscopic procedures.

Exposing risk factor score: ____

Step 2: Predisposing risk factors associated with patient

Clinical setting	Molecular	
	Inherited (3 points)	Acquired (3 points)
<input type="checkbox"/> Age 40 to 60 years (1 point)	<input type="checkbox"/> Factor V Leiden/activated	<input type="checkbox"/> Lupus anticoagulant
<input type="checkbox"/> Pregnancy or postpartum (<1 month; 1 point)	<input type="checkbox"/> Antithrombin III deficiency	<input type="checkbox"/> Antiphospholipid antibodies
<input type="checkbox"/> Varicose veins (1 point)	<input type="checkbox"/> Proteins C and S deficiency	<input type="checkbox"/> Myeloproliferative disorders
<input type="checkbox"/> Inflammatory bowel disease (1 point)	<input type="checkbox"/> Dysfibrinogenaemia	<input type="checkbox"/> Disorders of plasminogen and plasmin activation
<input type="checkbox"/> Obesity (BMI >25; 1 point)	<input type="checkbox"/> Homocysteinaemia	<input type="checkbox"/> Heparin-induced thrombocytopenia
<input type="checkbox"/> Combined oral contraceptive/hormonal replacement therapy (1 point)	<input type="checkbox"/> 20210A prothrombin mutation	<input type="checkbox"/> Hyperviscosity
<input type="checkbox"/> Age >60 years (2 points)		
<input type="checkbox"/> Malignancy (2 points)		
<input type="checkbox"/> Age >75 years (3 points)		
<input type="checkbox"/> History of DVT/PE (3 points)		

Predisposing risk factor score: ____

Step 3: Total risk factor score (Exposing + Predisposing): ____

guidelines on appropriate VTE prophylaxis and treatment. These guidelines strictly adhere to an evidence-based approach and are often cited as standard of care ³³. The ACCP categorises patients according to the type of hospital service that is providing care and makes graded recommendations for each group with regard to the benefits and risks of specific options ¹. Table 3 details the different grades that are assigned and the rationale behind each grade.

General surgery

Table 4 summarises the 2004 ACCP recommendations for VTE prophylaxis in general surgery ¹. Two pharmacologic regimens, low-dose unfractionated heparin (LDUH) and low-molecular-weight heparins (LMWHs), are recommended (grade 1A) for use in moderate- and high-risk patients. High-risk doses (5000 U TID vs BID for LDUH and >3400 U QD vs ≤3400 U QD for LMWH) are recommended in high-risk patients. These recommendations are based on the results of randomised clinical trials demonstrating that both agents reduce the risk of both asymptomatic and symptomatic VTE in general surgery by at least 60% and have similar bleeding rates ^{1, 13, 15, 35-43}. No study reported a difference in the rate of symptomatic VTE between the two regimens ¹.

Mechanical prophylaxis alone has not been well studied in general surgery; therefore, mechanical prophylaxis alone is only recommended in patients at high risk for bleeding (grade 1A) ¹. Studies have demonstrated lower rates of VTE with mechanical plus pharmacologic prophylaxis compared with pharmacologic alone ⁴⁴⁻⁴⁶; therefore, in patients at the highest risk for VTE (those with multiple risk factors), mechanical prophylaxis (graduated compression stockings [GCS] or intermittent pneumatic compression [IPC]) in conjunction with pharmacologic prophylaxis is recommended (grade 1C+). Finally, extended prophylaxis (two to three weeks) with LMWH is recommended (grade 2A) in selected high-risk patients, such as those who have undergone major cancer surgery, based on data from three clinical trials ⁴⁷⁻⁵⁰.

At the time the 2004 ACCP guidelines were published, fondaparinux, the selective inhibitor of factor Xa, was not approved in the USA for use in general surgery and was, therefore, not given a recommendation.

Table 3 ACCP grades of recommendation for antithrombotic agents *.
Reproduced with permission from Guyatt *et al* ³⁴.

Grade of recommendation	Clarity of risk/benefit	Methodological strength of supporting evidence	Implications
1A	Clear	RCTs without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1C+	Clear	No RCTs, but RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1B	Clear	RCTs with important limitations (inconsistent results, methodological flaws†)	Strong recommendations; likely to apply to most patients
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence is available
2A	Unclear	RCTs without limitations	Intermediate-strength; best action may differ depending on circumstances or patient's societal values
2C+	Unclear	No RCTs but strong RCT results can be unequivocally extrapolated, or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or societal values
2B	Unclear	RCT with important limitations	Weak recommendation; alternatives likely better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendation; other alternatives may be equally reasonable

*Because studies in categories B and C are flawed, it is likely that most recommendations in these classes will be level 2. The following considerations will bear on whether the recommendation is Grade 1 or Grade 2: the magnitude and precision of the treatment effect; patients' risk of the target event being prevented; the nature of the benefit and the magnitude of the risk associated with treatment; variability in patient preferences; variability in regional resource availability and healthcare delivery practices; and cost considerations. Inevitably, weighing these considerations involves subjective judgment.

†These situations include RCTs with both lack of blinding and subjective outcomes, where the risk of bias in measurement of outcomes is high, or RCTs with large loss to follow-up.

RCT = randomised controlled trial

Table 4 ACCP VTE prophylaxis recommendations in general surgery ¹.

Regimen	Low risk ¹ (minor surgery, <40 years of age)	Moderate risk (minor surgery, 40-60 years of age or additional risk factors OR surgery, <40 years of age)	High risk (minor surgery, >60 years of age or additional risk factors OR surgery, >40 years of age or additional risk factors)	Highest risk (surgery with multiple risk factors)
LDUH (5000 U BID)	-	1A	-	-
LDUH (5000 U TID)	-	-	1A	1A
LMWH (≤3400 U QD)	-	1A	-	-
LMWH (>3400 U QD)	-	-	1A	1A
Extended LMWH (2-3 weeks)	-	-	2A ²	2A ²
Mechanical prophylaxis (GCS or IPC)	-	- ³	- ³	1C+ ⁴

1 The use of specific prophylaxis other than early and persistent mobilisation is not recommended in low-risk general surgery patients (grade 1C+).

2 In selected high-risk general surgery patients, including those who have undergone major cancer surgery, post-hospital discharge prophylaxis with LMWH is recommended.

3 In general surgery patients at moderate to high risk for VTE with a high risk of bleeding, the use of mechanical prophylaxis with properly fitted GCS or IPC, at least initially until the bleeding risk decreases, is recommended (grade 1A).

4 In high-risk general surgery patients with multiple risk factors, it is recommended that mechanical prophylaxis be combined with the use of GCS and/or IPC.

LMWH = low-molecular-weight heparin, LDUH = low-dose unfractionated heparin, IPC = intermittent pneumatic compression, GCS = graduated compression stockings, - = no specific recommendation made, IPC = Intermittent pneumatic compression, QD = daily, BID = twice per day, TID = three times per day

However, fondaparinux has since been approved in the USA for prophylaxis in abdominal surgical patients undergoing general anaesthesia for longer than 45 minutes, who are older than 40 years of age and have one of the following risk factors: neoplastic disease, obesity, chronic obstructive pulmonary disease, inflammatory bowel disease, history of DVT or PE, or congestive heart failure. In addition, it is indicated for abdominal surgical patients undergoing general anaesthesia lasting longer than 45 minutes who are older than 60 years of age with or without one or more of the risk factors listed above. This indication was based on two independent trials including one study demonstrating that postoperative fondaparinux (2.5mg daily) was at least as safe and effective as LMWH (5000 IU daily) in high-risk abdominal surgical patients⁵¹. In a subset analysis of this study in patients with cancer, fondaparinux significantly ($p=0.02$) reduced the incidence of VTE compared with LMWH, without increasing major bleeding. In the other trial with fondaparinux in abdominal surgery, IPC alone had a very low incidence of venographic VTE events (5.3%); however, IPC plus fondaparinux significantly reduced the incidence of venographic events to 1.7% ($p=0.004$)⁴⁶.

Orthopaedic surgery

Table 5 summarises the 2004 ACCP recommendations for VTE prophylaxis in orthopaedic surgery. All patients undergoing major orthopaedic surgery on a lower limb (total knee replacement [TKR], total hip replacement [THR], hip fracture surgery [HFS], or knee arthroscopy) are known to be at risk for VTE. Each surgery places the patient at a different risk for VTE. Data on which the recommendations are based were sufficient to recommend at least one prophylactic regimen (fondaparinux, LMWHs, or warfarin) supported by 1A evidence for short-term prophylaxis in THR, TKR, and HFS¹. Reductions in prevalence of DVT associated with these anticoagulant regimens are summarised in Figure 1^{13, 52-55}.

Table 5 ACCP VTE prophylaxis recommendations in orthopaedic surgery ¹.

Regimen	Total hip replacement (≥10 d/28-35 d)	Total knee replacement ¹ (≥10 d)	Knee arthroscopy (high risk) ⁶ (≥10 d)	Hip fracture surgery (≥10 d/28-35 d)
Fondaparinux ²	1A/1C+	1A	-	1A/1A
LMWH ³	1A/1A	1A	2B	1C+/1C+
Warfarin ⁴	1A/1A	1A	-	2B/1C+
Mechanical prophylaxis	1A against ⁵			
IPC		1B	-	1C+ if
GCS		-		anticoagulant
VFP		1A against ⁵		contra-indicated
Aspirin	1A against ⁵	1A against ⁵	-	1A against ⁵
LDUH	1A against ⁵	1A against ⁵	-	1B/-

1 Extended prophylaxis in knee replacement is not presently recommended.

2 2.5mg started 6 to 8 hours postoperatively.

3 For hip replacement: high-risk dose started 12 hours pre- or postoperatively OR half usual high-risk dose 4 to 6 hours postoperatively continued next day at full dose. For knee replacement and hip fracture: usual high-risk dose.

4 Adjusted to INR 2.5 (range 2-3), started pre-operatively or evening after surgery.

5 Not recommended as sole prophylaxis.

6 Prophylaxis following surgery is only recommended in patients at high risk for VTE.

LMWH = low-molecular-weight heparin, LDUH = low-dose unfractionated heparin, IPC = intermittent pneumatic compression, GCS = graduated compression stockings, VFP = venous foot pump, - = no specific recommendation made.

Mechanical prophylaxis alone was recommended as an alternative in TKR (grade 1B) and in HFS (grade 1C+) when anticoagulants are contra-indicated due to a high bleeding risk or as an adjunct to pharmacologic prophylaxis (grade 2A). It is also recommended (grade 1C+) that the proper use of, and optimal compliance with, the mechanical device is ensured. In addition, routine prophylactic use was not recommended (grade 2B) for use in patients undergoing knee arthroscopy who are not at increased risk for VTE (no pre-existing VTE risk factors, or surgery is not prolonged or complicated).

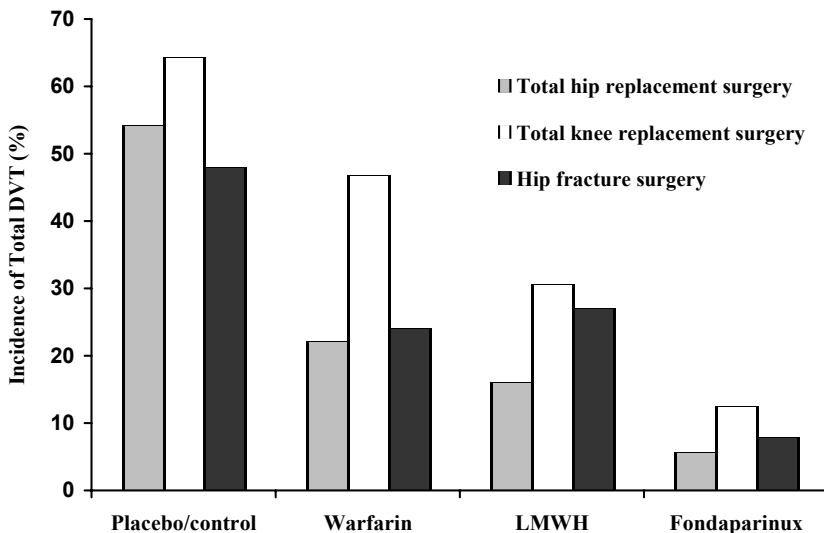


Figure 1 Reductions in DVT prevalence with VTE prophylaxis.

It was recommended (grade 1A) that the timing of the first dose of prophylaxis should be decided by weighing the effect of timing on risk of bleeding with its effect on the efficacy of each particular agent¹. The effect of timing on the efficacy/bleeding ratio of each agent is not known; however, it is acceptable to use LMWHs either pre-operatively or postoperatively (grade 1A). Duration of prophylaxis in THR, TKR, and HFS was recommended to be at least ten days (grade 1A). Extended prophylaxis (up to 28 to 35 days) was recommended in THR and HFS (grade 1A). Fondaparinux was the only grade 1A recommended option for extended prophylaxis in HFS, and the grade 1A recommendations for extended prophylaxis in THR were LMWH and warfarin.

Medical patients

In acutely ill medical patients who have been admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined

to bed and have one or more additional risk factors, prophylaxis with LDUH or LMWH is strongly recommended (grade 1A). Several studies evaluated these agents in medical patients and demonstrated significant reductions in the relative risk of DVT by approximately 70% compared with placebo, without increased risk of bleeding^{16-20, 22}. In the most recent study, the PREVENT trial, LMWH significantly reduced the incidence of VTE by nearly 50%²². Of five studies that compared LDUH and LMWH in medical patients, four failed to find significant differences in DVT rates or bleeding between agents⁵⁶⁻⁵⁹. One study reported a significantly lower incidence of DVT with 40mg LMWH QD compared with 5000 U LDUH TID (15.6% vs 22.1%, $p=0.04$)⁶⁰.

Fondaparinux is not approved in the USA for use in medical patients; however, it has been shown to significantly ($p=0.029$) reduce the incidence of both VTE and fatal PE by nearly 50% compared with placebo, without increased major bleeding, in hospitalised patients with acute medical illness⁶¹. All of these agents (LDUH, LMWH and fondaparinux) significantly reduce the incidence of VTE in medical patients when compared with placebo. Thus, it is no longer valid not to use VTE prophylaxis in this patient population.

Mechanical prophylaxis (GCS or IPC) is recommended (grade 1C+) in medical patients with risk factors for VTE and in whom there is a contraindication to anticoagulant prophylaxis. Although no randomised clinical trials have evaluated mechanical prophylaxis alone in medical patients, a recently completed trial in general surgery in the USA demonstrated a low incidence of VTE (5.3%) with IPC alone in moderate-risk patients and has provided an impetus for their use in this patient population⁴⁶. Another recent trial in the prevention of VTE in stroke patients showed superior efficacy for the combination of anti-embolism stockings plus IPC compared with stockings⁶².

Advantages and disadvantages of methods of VTE prophylaxis

Although mechanical methods of prophylaxis are attractive options in patients who have a high risk of bleeding, practical limitations include a lack of standardisation of the quality of the stockings, difficulty with fitting patients with unusual limb sizes or shapes, and poor compliance with their

use by both healthcare providers and patients^{63, 64}. The different available pharmacologic agents for VTE prophylaxis are compared in Table 6. The biggest advantage of warfarin is oral administration. Additional advantages include low cost, reversal of effects by vitamin K, no dose adjustment required with renal failure, and a slightly reduced risk of surgical-site bleeding and wound hematoma. Disadvantages include delayed onset of action, monitoring requirements, a common failure to achieve the desired international normalised ratio (INR), many dietary and drug interactions, a contra-indication in patients at risk for bleeding, and a bleeding risk with extended prophylaxis.

LDUH was the first pharmacologic agent widely investigated for the prevention of VTE and has a long history of use. Other advantages of LDUH are reversal by protamine sulphate and low cost relative to LMWH and fondaparinux. A limitation of LDUH is its association (up to a 5% incidence) with heparin-induced thrombocytopenia (HIT), an antibody-mediated process characterised by a dramatic drop in platelets⁷⁷⁻⁷⁹. HIT can result in significant morbidity, including limb ischaemia resulting in limb loss and is associated with a mortality rate of 12% to 23%^{80, 81}. HIT is associated with all heparins (LDUH and LMWHs), although it is more frequent with LDUH, and use of heparins should be avoided in patients with HIT or a history of HIT^{77, 82}. Additional disadvantages of LDUH include intravenous administration requiring hospitalisation and a short half-life (half an hour to two hours) relative to other anticoagulants, necessitating more frequent dosing. However, a short half-life can sometimes be an advantage in the case of bleeding complications or for the management of patients with renal failure.

Clinical advantages of LMWH over LDUH include once-daily, subcutaneous administration, and a lower risk of HIT⁷⁷. LMWHs also carry a risk for HIT and should not be used in patients with HIT or a history of HIT^{37, 43, 78, 83}. Additional advantages include a higher anti-Xa activity compared with antithrombin activity, better bioavailability at low doses, no monitoring required, and a longer half-life (four hours), allowing for once-daily dosing in some patients. However, a long half-life can sometimes be a disadvantage in the case of bleeding complications or renal failure. It has also been suggested that survival may be increased in patients with cancer, particularly those at early stages of malignancy, who receive

Table 6 Therapeutic modalities for the prevention and/or treatment of VTE 1, 12, 65-76.

Agent	Indications for use	Perceived advantages	Perceived disadvantages	Adverse effects (incidence)
Warfarin	<ul style="list-style-type: none"> Prophylaxis and/or treatment of VTE and its extension, and PE 	<ul style="list-style-type: none"> Oral administration No dose adjustment required with renal failure Effects neutralised by vitamin K Slightly reduced risk for surgical-site bleeding and wound haematoma, compared with LMWH in THR and TKR 	<ul style="list-style-type: none"> Regular monitoring is required due to its narrow therapeutic window Patients often fail to achieve therapeutic INR ranges Delayed onset of action (at least 3 days) Increased bleeding during extended prophylaxis Many drug and dietary interactions 	<ul style="list-style-type: none"> Major bleeding (2%) Skin necrosis; (<0.1%)
LDUH	<ul style="list-style-type: none"> Prophylaxis and treatment of VTE and its extension DVT and PE prophylaxis in patients undergoing major abdominothoracic surgery or who for other reasons are at risk of developing thrombo-embolic disease (in a low-dose regimen) 	<ul style="list-style-type: none"> Extensive clinical experience Immediate onset/offset of action Effects neutralised with protamine sulfate No dose adjustment required in patients with renal failure Inexpensive 	<ul style="list-style-type: none"> Low bioavailability (28.6% SC), short half-life (0.5-3 hours), non-specific binding, and rapid clearance Intravenous administration Therapeutic monitoring of aPTT and frequent dose adjustments are required Prolongs INR Contra-indicated in patients with severe thrombocytopenia HIT 	<ul style="list-style-type: none"> Major bleeding (0%-7%) Thrombocytopenia (0%-30%) HIT (1%-5%) Wound haematomas/infections (1%-4%) Heparin-induced osteopenia /osteoporosis (30% with prolonged use)

Continued:

Agent	Indications for use	Perceived advantages	Perceived disadvantages	Adverse effects (incidence)
LMWHs	<ul style="list-style-type: none"> VTE prophylaxis (enoxaparin and dalteparin only) 	<ul style="list-style-type: none"> 81 %-100% bioavailability, long half-life (1.7-7 hrs), and predictable dose response 	<ul style="list-style-type: none"> Dose adjustment required in patients with renal failure (CrCl <30mL/min) or increased BMI 	<ul style="list-style-type: none"> Major bleeding (1 %-4%)
Enoxaparin sodium	<ul style="list-style-type: none"> THR during and following hospital 	<ul style="list-style-type: none"> Laboratory monitoring not required in most patients 	<ul style="list-style-type: none"> May be less effective than LDUH in patients with a high BMI when given QD 	<ul style="list-style-type: none"> Thrombocytopenia (<1 %-3%) HIT (lower rates than seen with LDUH)
Dalteparin sodium	<ul style="list-style-type: none"> TKR (enoxaparin only) Abdominal surgery 	<ul style="list-style-type: none"> Effects partially neutralised with protamine sulphate 	<ul style="list-style-type: none"> May require anti-Xa activity monitoring in selected patients 	<ul style="list-style-type: none"> Wound haematomas/infections (2%-3%)
Tinzaparin sodium	<ul style="list-style-type: none"> Patients at risk for thrombo-embolic complications Medical patients at risk for thrombo-embolic complications due to acute illness 	<ul style="list-style-type: none"> QD dosing SC administration Survival benefit in patients with cancer 	<ul style="list-style-type: none"> Therapeutic range depends on once vs twice daily administration 	<ul style="list-style-type: none"> Heparin-induced osteopenia/osteoporosis (with prolonged use)
	<ul style="list-style-type: none"> VTE treatment (enoxaparin and tinzaparin only): Inpatient treatment of acute DVT with or without PE when administered in conjunction with warfarin Outpatient treatment of DVT without PE when administered in conjunction with warfarin (enoxaparin only) 			

Continued:

Table 6 continued:

Agent	Indications for use	Perceived advantages	Perceived disadvantages	Adverse effects (incidence)
Fondaparinux sodium	<ul style="list-style-type: none"> • VTE prophylaxis: <ul style="list-style-type: none"> - hip fracture surgery, including extended prophylaxis - THR and TKR - abdominal surgery with risk of thrombo-embolic complications • VTE treatment: <ul style="list-style-type: none"> - Acute DVT when administered in conjunction with warfarin - Acute PE when administered in conjunction with warfarin when initial therapy is administered in the hospital 	<ul style="list-style-type: none"> • 100% bioavailability, lack of non-specific binding, and long half-life (17 hours) • No evidence of HIT to date • QD dosing • SC administration • Can be administered on outpatient basis • Bleeding similar to LDUH and LMWHs • Improved wound healing compared with LMWHs 	<ul style="list-style-type: none"> • Contra-indicated in patients with severe renal impairment (CrCl <30mL/min) • Contra-indicated for prophylaxis in orthopaedic surgery in patients weighing <50kg • Long half-life • No reversal agent 	<ul style="list-style-type: none"> • Major bleeding (1%-3%)

VTE = venous thrombo-embolism, DVT = deep venous thrombosis, PE = pulmonary embolism, LDUH = low-does unfractionated heparin, LMWH = low-molecular-weight heparin, THR = total hip replacement, TKR = total knee replacement, HIT = heparin-induced thrombocytopenia, SC = subcutaneous, aPTT = activated partial thromboplastin time, INR = international normalised ratio, QD = once daily, BID = twice daily, CrCl = creatinine clearance.

LMWH compared with LDUH, although the reason for this is not clear⁸⁴⁻⁸⁷. Disadvantages of LMWHs include renal excretion (precluding use in patients with renal failure), increased cost relative to LDUH, and incomplete reversal by protamine sulfate⁸⁸.

Fondaparinux is a novel synthetic pentasaccharide⁸⁹. Because factor Xa inhibitors are a new class of agents, they do not have as strong a history of clinical use as LDUH and LMWH. However, fondaparinux has demonstrated similar efficacy in patients undergoing general surgery⁵¹ and greater efficacy than LMWH in VTE prophylaxis following total joint replacement^{53, 54} and hip fracture surgery⁵². An advantage of fondaparinux is that, unlike LDUH and LMWH, it has not been associated with HIT and can be used in patients with HIT or a history of HIT. In addition, fondaparinux is administered subcutaneously and has a 17-hour half-life, which allows for convenient, once-daily dosing, but is contraindicated for prophylaxis in patients weighing less than 50kg or renally impaired patients (creatinine clearance <30mL/min). Further, because fondaparinux does not interfere with thrombin binding, it has no negative effect on wound healing. Although the long half-life allows for convenient dosing, it can sometimes be a disadvantage in the case of bleeding complications. Fondaparinux is renally excreted and should not be used in patients with renal failure.

Selected highlights of VTE treatment with anticoagulation

2004 ACCP recommendations^{71, 90}

ACCP recommendations for the management of VTE are summarised in Table 7⁷¹. The currently recommended approach for treatment of acute DVT of the leg and acute non-massive PE is to start LDUH or LMWH and warfarin together upon diagnosis, and to discontinue heparin when the INR is stable and >2.0 (grade 1A). For patients with a high clinical suspicion of DVT or PE, treatment with anticoagulants while awaiting the outcome of diagnostic tests is recommended (grade 1C+) ⁷¹. Although safety and efficacy with LDUH and LMWH in the treatment of DVT and PE are similar⁹¹⁻⁹⁶, LMWH is recommended over LDUH for DVT (outpatient treatment when possible [grade 1C] and inpatient treatment when

Table 7 ACCP recommendations for VTE treatment.

Regimen	Initial treatment of acute DVT	Long-term treatment of acute DVT		Initial treatment of acute non-massive PE	Long-term treatment of acute PE	
		Idiopathic ⁸	Transient risk factor		Idiopathic ⁸	Transient risk factor
		Cancer ⁹	Cancer ⁹		Cancer ⁹	Cancer ⁹
IV LDUH ¹	1A ^{3,4}	-	-	1A ³	-	-
SC LDUH ¹	1A ⁵	-	-	-	-	-
LMWH ¹	1A (over LDUH) ⁶	-	1A, 3-6 months	1A (over LDUH)	-	1A, 3-6 months
Warfarin (with heparin) ²	1A ⁷	1A, 6-12 months	1A, 3 months	1A ⁷	1A, 6-12 months	1A, 3 months

1 Recommended duration of initial treatment is at least 5 days (grade 1C).

2 Dose should be adjusted to maintain a target INR of 2.5 (range, 3.1 to 4.0, grade 1A).

3 Administered by continuous infusion with dose adjustment to achieve and maintain an aPTT prolongation corresponding to plasma heparin levels from 0.3 to 0.7 IU/mL anti-Xa activity by the amidolytic assay (grade 1C+).

4 Recommended over LMWH in patients with severe renal failure (grade 2C).

5 Recommended initial dose is 35,000 U/24 h, with subsequent dosing to maintain the aPTT in the therapeutic range (grade 1C+)

6 Recommended over LDUH as an outpatient if possible (grade 1C), and as an inpatient if necessary (grade 1A).

7 Initiation of warfarin together with LMWH or LDUH on the first treatment day with discontinuation of heparin when the INR is stable and >2.0 is recommended (grade 1A).

8 Should be considered for indefinite anticoagulant therapy (grade 2A).

9 Anticoagulant therapy recommended indefinitely or until the cancer is resolved (grade 1C).

DVT = deep venous thrombosis, PE = pulmonary embolism, IV = intravenous, SC = subcutaneous, LDUH = low-dose unfractionated heparin, LMWH = low-molecular-weight heparin, aPTT = activated partial thromboplastin time, - = no recommendation made.

necessary [grade 1A]) and non-massive PE (grade 1A). This is primarily due to convenience of administration and cost savings associated with outpatient therapy or early hospital discharge ^{92, 97, 98}.

Since the 2004 ACCP guidelines were published, fondaparinux (5.0, 7.5, or 10.0mg once daily in patients weighing <50kg, 50-100kg, or >100kg, respectively) has been shown to be at least as effective as LMWH (1mg/kg twice daily) for the initial treatment of acute DVT ⁹⁹, and as effective as LDUH (continuous IV, ratio of the activated partial thromboplastin time [aPTT] to a control value, 1.5 to 2.5) for the initial treatment of acute PE, without increasing the risk for major bleeding ¹⁰⁰.

For DVT, routine thrombolysis with thrombolytics or catheter-directed thrombolysis, including venous thrombectomy, is not recommended (grade 1A), except in selected patients at risk for limb loss. In PE, thrombolytics are not recommended (grade 1C) except in haemodynamically unstable patients (grade 2B). Catheter extraction or fragmentation and pulmonary embolectomy are not recommended (grade 1C), except in selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy (grade 2C). Vena caval interruption is not recommended for initial treatment of VTE (grade 1A), except in patients with a contra-indication for anticoagulation or with recurrent VTE despite anticoagulation (grade 2C).

Warfarin is recommended for long-term treatment of acute VTE over other treatment options, except in the case of patients with cancer, when LMWH is recommended based on studies showing greater efficacy over warfarin ^{101, 102}. For patients with cancer, the recommended duration is three to six months with LMWH (grade 1A), with a grade 1C recommendation for treatment indefinitely or until the cancer is resolved. Treatment indefinitely (grade 2C) or for 12 months (grade 1C+) is recommended in patients with a first episode of VTE who have documented antiphospholipid antibodies or two or more thrombophilic conditions (e.g. combined factor V Leiden and prothrombin 20210 gene mutations). In patients with a first episode of VTE and documented deficiency of antithrombin, protein C, or protein S or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII

levels, treatment is recommended for six to 12 months (grade 1A) or indefinitely (grade 2C). Recommendations for duration of treatment assign a relatively high value to preventing recurrent thrombo-embolic events and a relatively low value to bleeding and cost.

Advantages and disadvantages of methods of VTE treatment

The advantages and disadvantages of the pharmacologic anticoagulants are summarised in Table 6. Some advantages and disadvantages specific to VTE treatment will be discussed. With IV LDUH, anti-Xa activity must be monitored to determine the dose required to achieve and maintain therapeutic aPTT. In contrast, routine monitoring with anti-factor Xa level measurements are not required with LMWH (grade 1A) or fondaparinux. In addition, LMWH and fondaparinux can be used on an outpatient basis, which can result in significant cost savings. A limitation of LMWH is that it is not well tested in massive PE; thus, the indication for LMWH in the USA is limited to the inpatient or outpatient treatment of DVT with or without PE in conjunction with warfarin and not for PE alone. In contrast, fondaparinux has been tested in PE alone and is indicated for the treatment of PE.

Precautions

Any drug that is renally excreted should be used with caution in renally impaired patients. Both LMWH and fondaparinux are renally excreted. Because exposure of LMWH is significantly increased in patients with severe renal impairment (creatinine clearance $<30\text{mL/min}$), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance $30\text{-}50\text{mL/min}$) and mild (creatinine clearance $50\text{-}80\text{mL/min}$) renal impairment. Fondaparinux should be used with caution in patients with moderate renal impairment and is contra-indicated in patients with severe renal impairment.

Over 20 case reports of spinal haematoma and paralysis have been reported with the use of LMWH in patients receiving neuraxial

anaesthesia¹⁰³, ultimately leading to an FDA-mandated 'black box' warning. Thus, caution is recommended regarding the use of antithrombotic drugs in patients having spinal puncture or placement of an epidural catheter (evidence Grade 1C+). The current ACCP guidelines outline some precautions:

- ◆ if using warfarin, continuous epidural catheterisation should not be used for longer than one to two days due to unpredictable anticoagulant effects, and the INR should be less than 1.5 at the time of catheter removal;
- ◆ prophylactic LMWH can be given with an epidural catheter in place but the drug must be stopped for 12 hours with a twice-daily dose and 24 hours with a once-daily dose before removing the catheter, and one must wait two hours before giving the next dose;
- ◆ when an epidural is used, fondaparinux should not be given until the epidural catheter has been removed for at least two hours and should not be administered to patients receiving continuous epidural spinal block, due to presently insufficient safety data;
- ◆ neuraxial blockade should generally be avoided in patients with clinical bleeding disorders;
- ◆ insertion of the spinal needle in patients receiving anticoagulants or platelet inhibitors should be delayed until medication effects are minimal;
- ◆ prophylaxis should be delayed if a haemorrhagic aspirate (bloody tap) is noted during initial needle placement;
- ◆ removal of epidural catheters should occur when anticoagulant effects are minimal; and
- ◆ anticoagulant prophylaxis should be delayed for at least two hours after spinal needle placement or catheter removal.

Conclusions

VTE is a common, serious condition that can be disabling and sometimes fatal. The consequences of VTE underscore the importance of prevention in patients at risk. Risk assessment is required in all patients undergoing general or orthopaedic surgery and in all hospitalised patients. Risk assessment can guide decisions for prophylaxis and treatment of VTE, and can result in improved outcomes.

Key Summary

- ◆ Venous thrombo-embolism is a serious disorder causing significant morbidity and mortality.
- ◆ The long-term consequences of this disease are generally unappreciated and unrecognised.
- ◆ Thrombosis prophylaxis is vastly underused, particularly in the medically ill patient.
- ◆ Individual patient risk assessment should guide the type, duration and intensity of thrombosis prophylaxis according to the level of patient risk.

References

1. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, *et al.* Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl): 338S-400S.
2. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, *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(5): 933-8.
3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158(6): 585-93.
4. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med* 1999; 159(5): 445-53.
5. Kniffin WD, Jr., Baron JA, Barrett J, Birkmeyer JD, Anderson FA, Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med* 1994; 154(8): 861-6.
6. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, *et al.* The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125(1): 1-7.
7. Prandoni P, Villalta S, Bagatella P, Rossi L, Marchiori A, Piccioli A, *et al.* The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997; 82(4): 423-8.
8. Goldhaber SZ. Pulmonary embolism. *N Engl J Med* 1998; 339(2): 93-104.

9. National Quality Forum. Safe practices for better healthcare: a consensus report. Washington DC; 2003.
10. Caprini JA, Arcelus JI, Reyna JJ. Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease. *Semin Hematol* 2001; 38(2 Suppl 5): 12-9.
11. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999; 353(9159): 1167-73.
12. Turpie AG, Chin BS, Lip GY. ABC of antithrombotic therapy: venous thromboembolism: treatment strategies. *BMJ* 2002; 325(7370): 948-50.
13. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, Jr., et al. Prevention of venous thromboembolism. *Chest* 2001; 119(Suppl 1): 132S-175S.
14. Kakkar VV, Corrigan TP, Fossard DP. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. *Lancet* 1975; 2(7924): 45-51.
15. Collins R, Scrimgeour A, Yusuf S, Peto R. 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(18): 1162-73.
16. Gallus AS, Hirsh J, Tuttle RJ, Trebilcock R, O'Brien SE, Carroll JJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. *N Engl J Med* 1973; 288(11): 545-51.
17. Belch JJ, Lowe GD, Ward AG, Forbes CD, Prentice CR. Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J* 1981; 26(2): 115-7.
18. Cade JF. High risk of the critically ill for venous thromboembolism. *Crit Care Med* 1982; 10(7): 448-50.
19. Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. *Haemostasis* 1986; 16(2): 159-64.
20. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, 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(11): 793-800.
21. Oger E, Bressollette L, Nonent M, Lacut K, Guias B, Couturaud F, et al. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. *Thromb Haemost* 2002; 88(4): 592-7.
22. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation* 2004; 110(7): 874-9.
23. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. *Arch Intern Med* 1992; 152(8): 1660-4.
24. Rosendaal FR. Risk factors for venous thrombotic disease. *Thromb Haemost* 1999; 82(2): 610-9.
25. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. *Arch Intern Med* 2002; 162(11): 1245-8.
26. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; 107(23 Suppl 1): 16-9.

27. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *BMJ* 1992; 305(6853): 567-74.
28. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, *et al.* Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. *Arch Intern Med* 2004; 164(9): 963-8.
29. Second Thromboembolic Risk Factors (THRIFT II) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *Phlebology* 1998; 13: 87-97.
30. Verstraete M. Prophylaxis of venous thromboembolism. *BMJ* 1997; 314(7074): 123-5.
31. Prevention of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). *Int Angiol* 1997; 16(1): 3-38.
32. Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, *et al.* Electronic alerts to prevent venous thromboembolism among hospitalized patients. *N Engl J Med* 2005; 352(10): 969-77.
33. Tapson VF. The evolution and impact of the American College of Chest Physicians consensus statement on antithrombotic therapy. *Clin Chest Med* 2003; 24(1): 139-51.
34. Guyatt G, Schunemann HJ, Cook D, Jaeschke R, Pauker S. Applying the grades of recommendation for antithrombotic and thrombolytic therapy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl): 179S-187S.
35. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. *Ann Surg* 1988; 208(2): 227-40.
36. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001; 88(7): 913-30.
37. Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DJ, Das SK, *et al.* Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. *Lancet* 1993; 341(8840): 259-65.
38. Nurmohamed MT, Verhaeghe R, Haas S, Iriarte JA, Vogel G, van Rij AM, *et al.* A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. *Am J Surg* 1995; 169(6): 567-71.
39. Bergqvist D, Burmark US, Frisell J, Hallbook T, Lindblad B, Risberg B, *et al.* Low molecular weight heparin once daily compared with conventional low-dose heparin twice daily. A prospective double-blind multicentre trial on prevention of postoperative thrombosis. *Br J Surg* 1986; 73(3): 204-8.
40. Bergqvist D, Matzsch T, Burmark US, Frisell J, Guilbaud O, Hallbook T, *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(9): 888-91.
41. 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. ENOXACAN Study Group. *Br J Surg* 1997; 84(8): 1099-103.

42. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, *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(3): 438-44.
43. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. *Br J Surg* 1997; 84(6): 750-9.
44. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* 2000; (3): CD001484.
45. Ramos R, Salem BI, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. *Chest* 1996; 109(1): 82-5.
46. Turpie AG, Bauer KA, Caprini J, Comp PC, Gent M, Muntz J. Fondaparinux combined with intermittent pneumatic compression (IPC) versus IPC alone in the prevention of VTE after major abdominal surgery: results of the APOLLO study [abstract]. *J Thromb Haemost* 2005; 3(Suppl 1): Abstract P1046.
47. Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M, *et al*. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. *Eur J Surg* 1998; 164(9): 657-63.
48. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, *et al*. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002; 346(13): 975-80.
49. Rasmussen MS. Preventing thromboembolic complications in cancer patients after surgery: a role for prolonged thromboprophylaxis. *Cancer Treat Rev* 2002; 28(3): 141-4.
50. Rasmussen MS, Willie-Jorgensen P, Jorgensen LN. Prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) following major abdominal surgery for malignancy [abstract]. *Blood* 2003; 102: 56a.
51. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg* 2005; 92(10): 1212-20.
52. Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. *N Engl J Med* 2001; 345(18): 1298-304.
53. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med* 2001; 345(18): 1305-10.
54. Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002; 359(9319): 1715-20.
55. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. *Lancet* 2002; 359(9319): 1721-6.

56. 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(4): 529-34.
57. Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. *Haemostasis* 1996; 26(3): 127-39.
58. Lechler E, Schramm W, Flosbach CW. The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. *Haemostasis* 1996; 26 Suppl 2: 49-56.
59. Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW. 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(4): 614-21.
60. Harenberg J, Schomaker U, Flosbach CW. Enoxaparin is superior to unfractionated heparin in the prevention of venous thromboembolic events in medical patients at increased thromboembolic risk. *Blood* 1999; 94(Suppl 1): 399a.
61. Cohen AT, Davidson BL, Gallus A, Lassen MR, Tomkowski W, Turpie AG, *et al*. Fondaparinux for the prevention of VTE in acutely ill medical patients [abstract]. *Blood* 2003; 102: 15a.
62. Lacut K, Bressollette L, Le Gal G, Etienne E, De Tinteniak A, Renault A, *et al*. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. *Neurology* 2005; 65(6): 865-9.
63. Comerota AJ, Katz ML, White JV. Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? *Am J Surg* 1992; 164(3): 265-8.
64. Cornwell EE, 3rd, Chang D, Velmahos G, Jindal A, Baker D, Phillips J, *et al*. Compliance with sequential compression device prophylaxis in at-risk trauma patients: a prospective analysis. *Am Surg* 2002; 68(5): 470-3.
65. Innohep (package insert). Boulder, CO: Pharmion Corporation, 2003.
66. ARIXTRA (package insert). Research Triangle Park, NC: GlaxoSmithKline, 2004.
67. Lovenox (package insert). Bridgewater, NJ: Aventis Pharmaceuticals, Inc., 2004.
68. Fragmin (package insert). Kalamazoo, MI: Pharmacia & Upjohn Company, 2004.
69. Heparin sodium (package insert). Kalamazoo, MI: Pharmacia & Upjohn Company, 2000.
70. Warfarin sodium (package insert). Pomona, NY: Barr Laboratories, Inc., 2002.
71. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl): 401S-428S.
72. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, *et al*. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001; 119(1 Suppl): 8S-21S.
73. Walenga JM, Frenkel EP, Bick RL. Heparin-induced thrombocytopenia, paradoxical thromboembolism, and other adverse effects of heparin-type therapy. *Hematol Oncol Clin North Am* 2003; 17(1): 259-82, viii-ix.
74. Hyers TM. Management of venous thromboembolism: past, present, and future. *Arch Intern Med* 2003; 163(7): 759-68.

75. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, *et al.* Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001; 134(3): 191-202.
76. Ginsberg JS. Management of venous thromboembolism. *N Engl J Med* 1996; 335(24): 1816-28.
77. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, *et al.* Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995; 332(20): 1330-5.
78. Warkentin TE, Levine M, Hirsh J, Klama LN, Kelton JG. Formation of heparin-induced thrombocytopenia IgG without thrombocytopenia: analysis of a clinical trial (abstract). *Blood* 1995; 86(Suppl 1): 537a.
79. King DJ, Kelton JG. Heparin-associated thrombocytopenia. *Ann Intern Med* 1984; 100(4): 535-40.
80. Silver D, Kapsch DN, Tsoi EK. Heparin-induced thrombocytopenia, thrombosis, and hemorrhage. *Ann Surg* 1983; 198(3): 301-6.
81. Laster J, Cikrit D, Walker N, Silver D. The heparin-induced thrombocytopenia syndrome: an update. *Surgery* 1987; 102(4): 763-70.
82. Martel N, Lee J, Wells PS. Risk of heparin-induced thrombocytopenia with unfractionated and low molecular weight heparin thromboprophylaxis: a meta-analysis. *Blood* 2005; Epub 28 Jun 2005.
83. Hirsh J, Warkentin TE, Raschke R, Granger C, Ohman EM, Dalen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1998; 114(5 Suppl): 489S-510S.
84. von Tempelhoff GF, Harenberg J, Niemann F, Hommel G, Kirkpatrick CJ, Heilmann L. 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(4): 815-24.
85. Green D, Hull RD, Brant R, Pineo GF. Lower mortality in cancer patients treated with low-molecular-weight versus standard heparin. *Lancet* 1992; 339(8807): 1476.
86. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, *et al.* Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992; 326(15): 975-82.
87. Kakkar AK, Levine MN, Kadziola Z, Lemoine NR, Low V, Patel HK, *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(10): 1944-8.
88. Sugiyama T, Itoh M, Ohtawa M, Natsuga T. Study on neutralization of low molecular weight heparin (LHG) by protamine sulfate and its neutralization characteristics. *Thromb Res* 1992; 68(2): 119-29.
89. Bauer KA. Fondaparinux sodium: a selective inhibitor of factor Xa. *Am J Health Syst Pharm* 2001; 58(Suppl 2): 14-17.
90. Weitz JI, Hirsh J, Samama MM. New anticoagulant drugs: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126(3 Suppl): 265S-286S.

91. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000; 160(2): 181-8.
92. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. *N Engl J Med* 1997; 337(10): 657-62.
93. Hull RD, Raskob GE, Brant RF, Pineo GF, Elliott G, Stein PD, *et al.* Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. American-Canadian Thrombosis Study Group. *Arch Intern Med* 2000; 160(2): 229-36.
94. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, *et al.* A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. *N Engl J Med* 1997; 337(10): 663-9.
95. de Valk HW, Banga JD, Wester JW, Brouwer CB, van Hessen MW, Meuwissen OJ, *et al.* Comparing subcutaneous danaparoid with intravenous unfractionated heparin for the treatment of venous thromboembolism. A randomized controlled trial. *Ann Intern Med* 1995; 123(1): 1-9.
96. Meyer G, Brenot F, Pacouret G, Simonneau G, Gillet Juvin K, Charbonnier B, *et al.* Subcutaneous low-molecular-weight heparin fragmin versus intravenous unfractionated heparin in the treatment of acute non-massive pulmonary embolism: an open randomized pilot study. *Thromb Haemost* 1995; 74(6): 1432-5.
97. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, *et al.* A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; 334(11): 677-81.
98. Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, *et al.* Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med* 1996; 334(11): 682-7.
99. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, *et al.* Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004; 140(11): 867-73.
100. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, *et al.* Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003; 349(18): 1695-702.
101. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, *et al.* Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349(2): 146-53.
102. Hull R, Pineo G, Mah A. A randomised trial evaluating long-term low-molecular-weight heparin therapy for three months vs intravenous heparin followed by warfarin sodium in patients with current cancer. *Thromb Haemost* 2003; (suppl): P137a.
103. Horlocker TT, Heit JA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthetic management. *Anesth Analg* 1997; 85(4): 874-85.