Chapter 12
The prophylaxis and treatment of venous thrombo-embolism

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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 2003 [9]. 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 prophylaxis [10]. 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 VTE [10].

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 therapy [1]. 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 VTE [32]. 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
☐ Minor surgery	☐ Major surgery* ☐ Immobilizing plaster cast ☐ Patients confined to bed >72 hours ☐ Central venous access ☐ Arthroscopic surgery	☐ Myocardial infarction ☐ Congestive heart failure ☐ Severe sepsis/ infection	☐ Elective major lower extremity arthroplasty ☐ Hip, pelvis, or leg fracture (<1 month) ☐ Stroke (<1 month) ☐ Multiple trauma (<1 month) ☐ 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

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

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 patients [51]. 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 HFS [1]. 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).

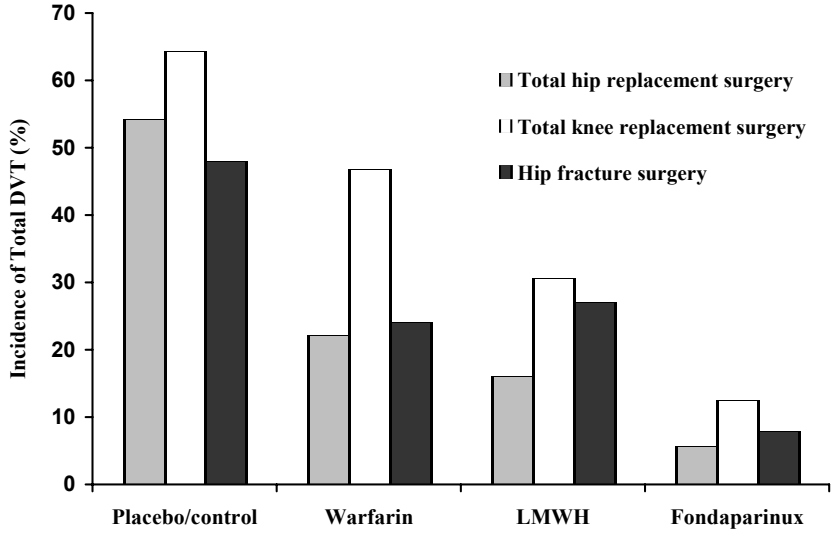

Figure 1 Reductions in DVT prevalence with VTE prophylaxis.

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 agent [1]. 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 agents [56-59]. 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 illness [61]. 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 contra-indication 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 population [46]. 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 stockings [62].

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 platelets [77-79]. 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 HIT [77]. 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	• Prophylaxis and/or treatment of VTE and its extension, and PE	• 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	• 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	• Major bleeding (2%) • Skin necrosis; (<0.1%)
LDUH	• Prophylaxis and treatment of VTE and its extension • DVT and PE prophylaxis in in patients undergoing major abdominothoracic surgery or who for other reasons are at risk of developing thrombo-embolic disease (in a low-dose regimen)	• Extensive clinical experience • Immediate onset/offset of action • Effects neutralised with protamine sulfate • No dose adjustment required in patients with renal failure • Inexpensive	• 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	• 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 Enoxaparin sodium Dalteparin sodium Tinzaparin sodium	• VTE prophylaxis (enoxaparin and dalteparin only) - THR during and following hospital - TKR (enoxaparin only) - Abdominal surgery patients at risk for thrombo-embolic complications - Medical patients at risk for thrombo-embolic complications due to acute illness • 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)	• 81%-100% bioavailability, long half-life (1.7-7 hrs), and predictable dose response • Laboratory monitoring not required in most patients • Effects partially neutralised with protamine sulphate • QD dosing • SC administration • Survival benefit in patients with cancer	• Dose adjustment required in patients with renal failure (CrCl <30mL/min) or increased BMI • May be less effective than LDUH in patients with a high BMI when given QD • May require anti-Xa activity monitoring in selected patients • Therapeutic range depends on once vs twice daily administration	• Major bleeding (1%-4%) • Thrombocytopenia (<1%-3%) • HIT (lower rates than seen with LDUH) • Wound haematomas/infections (2%-3%) Heparin-induced osteopenia/ osteoporosis (with prolonged use)

Continued:

Table 6 *continued:*

Agent	Indications for use	Perceived advantages	Perceived disadvantages	Adverse effects (incidence)
Fondaparinux sodium	• VTE prophylaxis: - hip fracture surgery, including extended prophylaxis - THR and TKR - abdominal surgery with risk of thrombo-embolic complications • VTE treatment: - Acute DVT when administered in conjunction with warfarin - Acute PE when administered in conjunction with warfarin when initial therapy is administered in the hospital	• 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	• 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	• 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 clear [84-87]. Disadvantages of LMWHs include renal excretion (precluding use in patients with renal failure), increased cost relative to LDUH, and incomplete reversal by protamine sulfate [88].

Fondaparinux is a novel synthetic pentasaccharide [89]. 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 surgery [51] and greater efficacy than LMWH in VTE prophylaxis following total joint replacement [53, 54] and hip fracture surgery [52]. 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 contra-indicated 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 7 [71]. 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 similar [91-96], 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	Cancer [9]		Idiopathic [8]	Transient risk factor	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 <30mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50mL/min) and mild (creatinine clearance 50-80mL/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

anaesthesia [103], 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.

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