State-of-the-art venous thromboembolism prophylaxis

SUMMARY

Effective pharmacologic and physical methods for the prevention of venous thromboembolism (VTE) are widely available. Yet, a significant proportion of patients develop VTE because prophylaxis is currently underutilized or, more frequently, because the intensity of prophylaxis is not adequate according to the level of thrombotic risk. In this regard, epidemiological studies have identified groups of medical and surgical patients at very high risk of developing VTE. Most of these patients present several risk factors that make them especially prone to develop thromboembolic complications. A number of clinical risk assessment models have been devised in order to categorize the potential VTE risk of a patient and select the most appropriate prophylaxis, according to the estimated risk.

Based on available evidence from published data, most medical and surgical patients will be adequately protected from VTE by the use of low-molecular-weight heparins (LMWHs). Mechanical modalities of prophylaxis, such as graduated compression stockings and intermittent pneumatic compression of the legs, could be indicated in moderate risk patients, particularly in those at high risk of bleeding. In patients at high risk, increasing doses of LMWHs or a combination of pharmacologic and mechanical methods should be considered. Novel anticoagulants such as direct thrombin inhibitors or factor Xa inhibitors may offer improved protection for patients who remain at risk despite the use of the prophylaxis currently available.

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The problem of venous thromboembolism

Venous thromboembolism (VTE) remains an important cause of morbidity and mortality. Pulmonary embolism (PE) is responsible for approximately 50,000 deaths in the United States every year. Most patients who die of fatal PE do so within 30 minutes of the acute event, without enough time to provide treatment.[1] On the other hand, recent data indicate that survival rates after VTE are lower than previously reported, with less than 60% and 50% of patients surviving at one week and one year after presenting PE, respectively.[2] Among those patients who survive an acute PE, almost 1% will develop chronic pulmonary hypertension.[3] Deep vein thrombosis (DVT) also causes significant long-term morbidity because of the development of chronic venous insufficiency (CVI) of the lower limbs, the post-thrombotic syndrome, which affects about 29% of patients eight years after DVT diagnosis. Similarly, approximately 30% of patients present with recurrent DVT after 8 years.[4]

Some groups of patients have a higher risk of VTE. In most of these cases, risk factors such as surgery, cancer, trauma, or immobilization can be identified.[5] Yet, other patients present with idiopathic VTE, and have no apparent clinical risk factors. In these cases, a hypercoagulable state (thrombophilia), acquired or congenital, might be responsible for the VTE.[6] The most important hemostatic abnormalities associated with a higher risk of VTE include activated protein C resistance secondary to factor V mutation (factor V Leiden),[7] deficiency of antithrombin, protein C and S,[6] G20210A prothrombin mutation,[8] antiphospholipid antibodies,[9] hyperhomocysteinemia[10] and, more recently, increased levels of factor V.[11,12]

Table 1. Definition of thromboembolic risk categories.

Category	Frequency of calf DVT (%)	Frequency of proximal DVT (%)	Frequency of fatal PE (%)
Highest risk	40-80	10-20	1-5
High risk	20-40	4-8	0.4-1
Moderate risk	10-20	2-4	0.1-0.4
Low risk	2	0.4	0.002

Modified from Clagett et al.[13]

DVT=deep vein thrombosis; PE=pulmonary embolism.

Table 2. Venous thromboembolism prevalence range after orthopedic and general major surgery.

	%DVT	%Prox DVT	%PE	%Fatal PE
THR	45-57	23-36	0.7-30	0.34-6
TKR	40-84	9-20	1.8-7	0.2-0.7
Hip fracture	30-60	17-36	4.3-24	3.6-13
General surgery	19-29	6-8	1.3-1.9	0.7-1.1

Modified from Clagett GP et al.[13]
DVT=deep vein thrombosis; PE=pulmonary embolism.
THR=total hip replacement; TKR=Total knee replacement.

Risk factor assessment has become most important, not only for the identification of candidates to receive prophylaxis, but also to select those patients at very high thrombotic risk, in whom more intense prophylaxis should be utilized.

Patients at risk

According to the fifth ACCP Consensus Conference on VTE prevention, application of effective prophylaxis depends on knowledge of specific clinical risk factors in individual patients.[13] This Conference has classified the level of VTE risk into four categories, depending on the expected rates of DVT and PE (Table 1). Most studies addressing the prevalence of VTE have involved surgical patients. Among those, orthopedic patients undergoing total hip or knee replacement are considered at the highest risk, as 40-80% of patients will develop postoperative DVT if prophylaxis is not implemented (Table 2).[13] Although most of these thrombi are asymptomatic, almost one-third will extend proximally and result in symptomatic DVT and PE (Figure 1). Recent studies have revealed that orthopedic patients undergoing "minor" procedures such as knee arthroscopy or receiving plaster casts because of closed leg injuries also have a noticeable thrombotic risk and are candidates to receive VTE prophylaxis (Table 3).[14-17]

Other surgical patients with very high VTE risk include those undergoing major abdominal or pelvic surgery, especially for cancer, and multiple trauma patients (Table 4).[13] There are also medical conditions associated with increased risk of DVT and PE. Two necropsy reviews have demonstrated that fatal PE is found more frequently in medical than in surgical patients.[18,19] This is not surprising since medical patients are usually older and frequently present a combination of risk factors.[20] The number of studies addressing the risk of VTE in medical patients is small and, in most cases, oriented to patient groups having specific problems such as myocardial infarction, cancer, and stroke. In this latter group, the risk of VTE is about 60%, similar to if not higher than that of orthopedic patients.[13, 21] Monreal and coworkers have documented a frequency of DVT of 60% in cancer patients with central venous access devices, especially in the upper extremities.[22] The rate of DVT in critically ill medical patients admitted to the intensive care unit (ICU) was close to 30%.[23] In a recent multicenter trial involving acutely ill medical patients admitted to hospital, the total rate of DVT was 15%, with one-third of the thrombi being proximal, when prophylaxis was not implemented.[24]

Patients suffering from multiple trauma also present an increased risk of VTE, especially those with spinal cord injury, pelvic or spine fracture resulting in prolonged immobilization. The risk is particularly high when there are several injuries affecting the lower extremities and

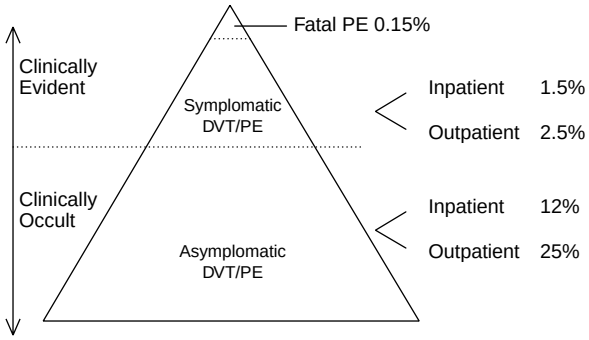

Figure 1. Spectrum of venous thromboembolism in patients undergoing total hip replacement.
(Adapted from Bruce Davidson, MD[154])
DVT=deep vein thrombosis; PE=pulmonary embolism.

Table 3. Venous thromboembolism prevalence after other orthopedic procedures and leg trauma.

Procedure	n	%DVT	%PE	Prophylaxis
Knee arthroscopy[14]	184	18	0	No
Knee arthroscopy[15]	101	8	0	Dalteparin
Plaster casts[16]	163	4.3	0	Placebo
	176	0	0	Mono-embolex
Plaster cast[17]	105	17	0	Placebo
	99	6	0	Fraxiparin

DVT=deep vein thrombosis; PE=pulmonary embolism.

head (77%) or spine (73%).[25] Data regarding the risk of patients undergoing minimally invasive procedures such as laparoscopic cholecystectomy are very limited since only a few studies have been conducted.[26,27] Nevertheless, surveys indicate that most surgeons performing these procedures use physical methods, heparin, or LMWH.[28,29]

Prophylactic methods

Pathogenesis of VTE is multifactorial as demonstrated by Rudolph Virchow in his classical triad. Apart from hypercoagulability and endothelial damage, venous stasis plays a major role for several reasons. First, stasis prevents the clearance of activated coagulation factors and reduces the mixing of those with their inhibitors. Second, in the presence of stasis there is local accumulation of adenosine diphosphate (ADP) derived from blood cells that can promote platelet aggregation.[30] In addition, when associated with venous dilatation, stasis may alter the normal linear blood flow, allowing platelets, red blood cells, and leukocytes to contact the endothelium. Venous stasis might reduce the release by the endothelium of activators of fibrinolysis. Finally, when stasis results in dilation of the vessels, cracks in the endothelium may develop which expose subendothelial collagen, which can trigger thrombosis.[31]

In most surgical patients, hypercoagulability and venous stasis represent the major factors predisposing to VTE. However, vascular wall damage may be important in patients undergoing certain orthopedic procedures such as hip or knee arthroplasty, and those suffering lower extremity trauma.

Because of the importance of hypercoagulability and venous stasis in the pathogenesis of VTE, pharmacological agents directed to correct hypercoagulability and mechanical methods designed to overcome stasis are a logical combination, especially for those patients at the highest risk.[13]

Table 4. Classification of level of venous thromboembolism risk.

Low	Moderate	High	Highest risk
Uncomplicated minor surgery in patients younger than 40 years No risk factors	Surgery in patients 40-60 years without RF Major surgery in <40 and no RF Minor surgery and RF	Major surgery in >60 years without RF Major surgery in >40 years and RF	Major surgery in >40 years + Previous VTE Malignancy Orthopedic surgery Thrombophilia Stroke or spinal cord injury Hip fracture

Modified from Clagett et al.[13]
RF=risk factors.

Table 5. Results of prophylaxis in general surgery.

Regimen	Trials	Enrollment	%DVT
Control	54	4310	25
LDH	53	9875	8
LMWH	17	8538	7
Dextran	11	872	18
IPC	5	313	10
GCS	4	300	9

Modified from Clagett et al.[13]
LDH=low dose heparin; LMWH=low-molecular-weight heparin.
IPC=Intermittent pneumatic compression. GCS=Graduated compression stockings.

Clinical experience with pharmacological prophylaxis

In patients undergoing general surgery, low dose unfractionated heparin (UFH) significantly reduces by more than 50% the rate of both postoperative DVT and fatal PE, with minimal bleeding, as shown in several meta-analyses of the literature.[32-34] Although other methods were also found to be effective in VTE prevention such as dextran, heparin-dihydroergotamine, and oral anticoagulants, they were associated with more complications and UFH became the standard for VTE prophylaxis in general surgery for more than a decade. Table 5 shows a list of a number of trials, patients and percentage of DVT over a range of prophylactic treatments.

In the eighties, a relatively new group of heparin fractions, generically known as LMWHs were accepted for clinical use. These heparin fractions have greater activity against factor Xa than does UFH, while their action against factor II remains similar to UFH. In this regard, experimental studies showed that LMWHs were able to prevent venous thrombosis without altering the coagulation mechanism to the same degree observed with UFH. In addition, these agents have better bioavailability and longer half-life that UFH when administered subcutaneously in low doses, which results in a more predictable anticoagulant response.[35] Therefore, LMWHs have practical advantages, including the possibility of a single daily injection without the need for laboratory monitoring, which makes these agents ideal for outpatient prophylaxis.

The efficacy of LMWHs has been demonstrated in a number of randomized control trials and subsequent meta-analyses in which LMWHs were compared with placebo and with UFH.[36-40] In general, the results of these studies indicate that LMWH and UFH are similar regarding their efficacy in preventing postoperative VTE (Table 5). Some studies have shown a marginal reduction in bleeding complications with LMWHs compared with UFH;[41] however, direct comparisons of bleeding

Table 6. Deep vein thrombosis prevalence as determined by venography after total hip replacement by prophylaxis group.

Regimen	Trials	Enrollment	%DVT
Control	13	655	51
LDH	10	653	31
Warfarin	7	898	22
LMWH	20	3016	15
Hirudin	3	1171	16
IPC	4	359	22

Modified from Clagett et al.[13]
LDH=low dose heparin; LMWH=low-molecular-weight heparin; IPC=intermittent pneumatic compression.

are difficult to evaluate because the rate of bleeding is dependent on the type of LMWH preparation and its dose. A real advantage of prophylaxis with LMWHs is the very low rate of heparin-induced thrombocytopenia associated with their use.[42] In addition, the incidence of heparin-induced osteoporosis has been reportedly lower using LMWH compared to UFH in patients receiving these drugs for three months.[43]

Several pharmacological methods have been evaluated in orthopedic surgery (Table 6). In patients undergoing total hip replacement, three meta-analyses showed greater reduction in the rate of postoperative VTE with LMWHs compared to UFH, without differences in the incidence of major bleeding.[36,37] On the other hand, most studies comparing LMWHs with warfarin showed that LMWHs are more effective than warfarin in preventing postoperative DVT.[44] However, this reduction in the rate of DVT achieved by these heparin fractions is offset by an increase in the incidence of bleeding complications.[45-47] A recent North American meta-analysis concludes that the best prophylactic agent, in terms of efficacy and safety, is warfarin. Yet, when compared to placebo no method reduced fatal PE.[48] Overall, LMWHs are easier to administer than are oral anticoagulants because no monitoring is required. Newer second-generation LMWHs such as bemiparin might be even more effective.[49]

In patients undergoing total knee replacement, LMWHs are superior to oral anticoagulants, although the incidence of DVT remains higher than 20%.[45,46,50,51] Another recent meta-analysis indicates that LMWHs are better than warfarin for the prevention of DVT.[52] No differences were found between the different prophylactic methods in the incidence of symptomatic pulmonary embolism. It is important to notice that, although evaluated together in the meta-analyses, LMWHs are distinct, non-interchangeable drugs. Indeed, the selection of the most appropriate LMWH for the prevention of VTE after total hip or total knee replacement should be based on the clinical trial evidence available for each individual drug.[53,54]

Patients suffering from hip fracture are at very high risk of both proximal DVT and PE (Table 2) and, accordingly, prophylaxis is recommended for all patients undergoing surgery for hip fracture.[13] Warfarin, UFH, and LMWHs are better than placebo in reducing postoperative DVT in these patients. A recent trial has documented a reduction in the incidence of symptomatic DVT and PE with the use of aspirin compared to placebo.[55] However, the results of this trial must be evaluated with caution since other pharmacologic prophylactic methods were used in more than 40% of the patients. Interestingly, in this trial aspirin did not reduce, compared to placebo, the incidence of postoperative VTE in patients undergoing elective hip or knee replacement. A previous controversial[56] meta-analysis indicated that aspirin was effective in most surgical populations.[57] At the present time aspirin is not generally recommended for VTE prophylaxis in general surgical or orthopedic patients.[13,21,58] A randomized trial has demonstrated that, as compared with UFH, a LMWH significantly reduced the rate of DVT in patients with major trauma with a low rate of major bleeding complications.[59]

Nonsurgical patients admitted to hospital are exposed to 5-50% DVT risk if prophylaxis is not implemented.[13,60] Recently, the Medenox and Prince trials have shown that enoxaparin, a LMWH, is better than placebo in acute medical patients,[24] and at least as effective as UFH in patients with severe respiratory disease and heart failure.[61] A recent meta-analysis has shown that both UFH and LMWHs are beneficial in the prevention of VTE in medical patients.[62] This study found that LMWHs and UFH have similar prophylactic efficiency but LMWHs are associated with a lower risk of major bleeding than UFH.

Clinical experience with mechanical methods of prophylaxis

Physical and mechanical methods of VTE prevention have not been as extensively studied as have some of the above-mentioned pharmacological modalities, but they represent an alternative approach for certain patient groups. These methods are directed primarily to overcoming venous stasis during and after surgery[31,63] and some of them also stimulate endothelial fibrinolytic activity.[64-66] The preferred modalities are graduated compression stockings and intermittent pneumatic compression (IPC) of the legs or the foot.

The use of graduated compression stockings (GCS) on the legs aims to reduce the cross-sectional area of the veins[67,68] and, by doing so, to prevent venous distension and to increase the velocity of blood flow.[69,70] The optimal pressure gradient profile consists of 18 mm Hg at the ankle, decreasing to 8 mm Hg in the upper thigh. Regarding the length of the stockings, most studies have used thigh-length GCS. Yet, one study did not find different DVT rates in patients undergoing abdominal

surgery and using above or below knee stockings.[71] Besides, below knee stockings are better tolerated by patients and are less expensive.[72]

Several trials including small numbers of patients have been performed, mostly in patients undergoing general abdominal surgery. Pooled analyses of these studies have reported a significant reduction in the rate of postoperative DVT inpatients receiving GCS compared to control patients without prophylaxis.[32,34] Another meta-analysis including 12 studies with sound methodology has concluded that using GCS results in a significant 68% risk reduction of DVT in moderate-risk general surgical patients.[73] A more recent analysis also suggests a 57% risk reduction after total hip replacement compared to control patients, without stockings.[74] Based on the available evidence, GCS should be considered as a single modality of VTE prophylaxis in low to moderate risk cases: patients under 40 years without additional risk factors undergoing uncomplicated general surgery.[13] This method is safe provided that it is used in patients without significant peripheral arterial disease, easy to use, and relatively inexpensive. In patients at higher risk of VTE, a combination of GCS with pharmacological methods should be considered, as will be discussed below.

IPC of the legs is the most extensively studied of the physical modalities and appears to be the most effective of these methods.[34,75] The results of trials conducted to assess IPC have been variable, depending on the type of surgery, patient risk factors, compression methodology applied, and endpoint used to detect VTE. Overall, most studies indicate that IPC is effective in reducing DVT after general surgery,[34,76,77] neurosurgery,[78] and orthopedic surgery.[79-82] Of the available mechanical methods, IPC is the most effective in orthopedic surgery; however, the incidence of proximal DVT is higher than with the best pharmacological options.[83]

Two studies have demonstrated the efficacy of IPC in the prevention of PE after total hip replacement[84] and cardiac surgery.[85] Furthermore, two recent meta-analyses have shown that IPC and warfarin represent good options in total hip replacement patients[48] and that IPC is similar to LMWH and better than warfarin for total knee replacement.[52] Because of the lack of serious side effects, IPC is particularly useful in patients at high risk of bleeding complications such as neurosurgery and pelvic surgery, or when pharmacological agents are contraindicated.[86]

IPC is contraindicated in patients with DVT since the thrombus could be partially or completely detached from the venous wall and embolized to the lungs. Therefore, DVT should be ruled out before applying IPC to immoblized patients at risk for VTE. This method should also be avoided in patients presenting with skin infections, severe peripheral arterial disease, and in patients with significant edema of the legs secondary to congestive heart failure. Other limitations of IPC include frequent nurse non-compliance both in regular and intensive care units because of improper placement of the compression sleeves or non-functional IPC devices.[87,88]

Intermittent pneumatic compression of the foot (IPCF) consists of an inelastic slipper or boot with an air bladder in the area of the sole of the foot that overlies the plantar venous reservoir. This air chamber is rapidly inflated to a pressure of 50-200 mm Hg over 3 seconds every 20 seconds.[89] This rapid plantar compression is capable of inducing a 250% increase in the blood velocity through the popliteal vein, also detectable at the femoral vein.[90]

Several studies documented a reduction in venographically detected DVT rates in orthopedic patients comparing the use of foot compression with no treatment.[91-93] More recent trials have reported better results with foot compression than with aspirin after total knee arthroplasty[94] and similar results of foot compression and a LMWH after total hip replacement.[95] However, two recent comparative trials have reported better results with LMWHs than with foot compression in patients undergoing total knee replacement.[96,97] Accordingly, there are limited data demonstrating a beneficial effect of the foot compression device both in orthopedic surgery and general surgery. Additionally, these foot pumps were not as effective as sequential compression for thrombosis prophylaxis in non-lower extremity trauma patients.[98]

Underuse of VTE prophylaxis

Recent North American and European consensus conferences have issued recommendations for VTE prophylaxis in different patient groups based on evidence provided by well-designed trials and meta-analyses of literature.[13,21,58,99] Yet, there is a lack of awareness of the VTE problem among physicians as shown by several surveys.[28,100,101] Only one-third of patients admitted to hospital received prophylaxis in central Massachusetts in 1991.[102] Similarly, 33% and 38% of patients received

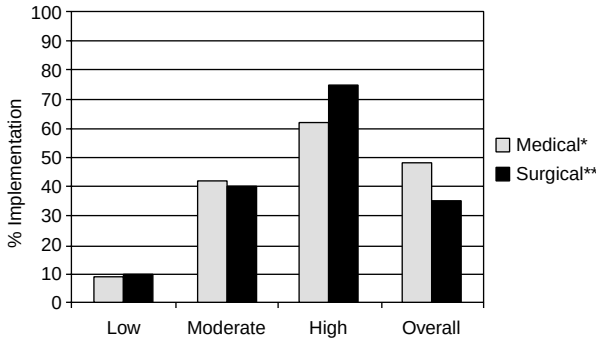

Figure 2. Implementation of prophylaxis among medical and general surgical patients at Glenbrook Hospital in patients at low, moderate, and high predicted risk to develop VTE and in the overall patient population. *Arcelus et al.[20] **Caprini et al.[105]

prophylaxis in the medical ICU and surgical ward, respectively.[103,104] In other studies involving over 1,000 consecutive hospital admissions, similar rates of prophylaxis implementation were found among medical and surgical patients (Figure 2).[20,105]

Physician practices regarding VTE prevention have changed, influenced by Consensus Guidelines. A very recent study in which more than 1,900 medical records were reviewed shows that more than 90% of patients receive prophylaxis following orthopedic surgery and 75% following high-risk major abdominal surgery.[106] However, only 50% of patients undergoing abdominal surgery received grade A prophylaxis according to the 1995 ACCP guidelines.[107]

Gillies and associates have identified three groups of surgical patients less likely to receive VTE prophylaxis: moderate-risk patients, emergency admissions, and patients treated conservatively.[108] The provision of clear and concise written prophylaxis protocols and the reinforcement of medical and nursing staffs' awareness of the VTE problem by internal audits or educational programs improve prevention practices.[109-111]

Improving the results of VTE prophylaxis

Recent meta-analyses of the literature have shown that LMWHs represent one of the best options to prevent VTE in general and orthopedic surgery.[36,37,39,44] However, the rates of total and proximal DVT remain high despite the utilization of LMWHs or oral anticoagulants in general[112] and orthopedic patients.[45,46,51] Even when the best available prophylaxis is given to patients undergoing total hip or knee replacement, 12-15% and 5-12% will present proximal thrombi, respectively.[45,46,51] Also of concern is that almost half of 52 surveyed British orthopedic surgeons, report that they discontinued the use of LMWH for total hip or knee replacement due to bleeding complications.[113]

There are a number of options to improve the results of VTE prevention, including a longer duration of prophylaxis, better risk assessment with a combined approach of physical and pharmacological agents in higher risk cases, and the development of novel antithrombotic drugs.

Duration of prophylaxis

The risk of developing VTE extends for several weeks after general and orthopedic surgery.[114-117] According to a recent review of medical charts in the state of California, the diagnosis of VTE was made after hospital discharge in 76% and 47% of patients undergoing THR and TKR, respectively.[118] These findings suggest that a more prolonged prophylaxis could be required in these patients. Warfarin is routinely used in the United States by many orthopedic surgeons several weeks after total hip replacement.[119-121]

Several European studies have demonstrated that extending the use of LMWH postoperatively 4-5 weeks after total hip replacement significantly reduces the rate of venographically detected DVT as compared to patients receiving LMWH only during their period of hospital admission.[122-125]

A recent North American trial has shown that extending LMWH prophylaxis 35 days after total hip replacement results in a significantly lower rate of total and proximal DVT compared with in-hospital warfarin.[126] Yet, another recent North American trial was not able to demonstrate a reduction of symptomatic objectively documented VTE after total hip replacement or total knee replacement in patients who received a different LMWH 6 weeks after surgery compared to those who received 4-10 days of postoperative LMWH.[127] On the other hand, some investigators do not support the use of extended prophylaxis based on good clinical outcomes in patients receiving in-hospital prophylaxis and a negative venogram or ultrasound at discharge after total hip replacement or total knee replacement.[128-131] The fifth ACCP Consensus Conference recommends 7-10 days of prophylaxis in patients undergoing total hip replacement, although prolonged prophylaxis should be considered in patients with ongoing risk factors.[13]

Risk stratification

Different factors contribute to VTE risk. These factors may be related to the clinical setting and to patient factors, either clinical or molecular. In many patients, several risk factors may be present and result in a very high risk derived from their cumulative effect. Risk factors are very prevalent among general surgical patients: 36% had three or more risk factors.[132] As mentioned above, risk of VTE varies between patients and clinical settings. Risk assessment will allow for a selective use of prophylaxis according to the actual risk level, using physical, pharmacological or both methods in combination, as required. This targeted approach will avoid undertreatment of very high-risk cases with "standard" prophylaxis, minimizing the risk of VTE and its sequelae and reducing the cost of treating long-term complications such as the post-thrombotic syndrome. A program of risk assessment will also avoid the use of unnecessary prophylaxis in low risk patients. This will reduce costs and avoid the risk of bleeding complications.

Several risk factor assessment (RAMs) models have been proposed to predict the thrombotic risk.[133-142] Physicians do not implement most of these models. One reason for this is the need to apply equations including non-routine laboratory tests to obtain some of these predictive indices. A recent review of preoperative homeostasis tests for the prediction of postoperative VTE concludes that, for the time being, they cannot be advocated for routine preoperative screening.[136] Accordingly, the ideal RAM should be easy to use and based on clinical risk factors, easy to identify from the patient's medical history and physical exam.[143,144] A very attractive simplified model has been proposed by a committee from the Paris Public Assistance Hospitals, which includes several charts for different surgical patients.[145]

The model developed from the fifth ACCP Consensus Conference includes four risk categories (Table 4).[13] The stratification of a patient into one of those categories is based exclusively on clinical information. In our opinion, a limitation of this RAM is that it does not provide a list of risk factors and, therefore, the physician has to remember a complete list of more than 20 factors to be able to categorize the risk of a particular patient. For this reason, we have modified our original risk assessment model and obtained a RAM that includes a list of risk factors,[105] with a scoring system that allows patients to be categorized into one of the four risk categories from the ACCP Consensus (Figure 3).[13]

Combination of mechanical and pharmacological methods

The use of a combination of pharmacological agents and graduated compression stockings has been found to be more effective than a single method in patients undergoing major abdominal surgery,[146] total hip replacement,[147,148] cardiac surgery,[85] and neurosurgery.[149-150]

A review of published trials comparing the use of heparin or LMWH alone or in combination with stockings indicates that the combination of physical and pharmacological methods is more effective in general and orthopedic surgery.[74] Similarly, the above-mentioned Pulmonary Embolism Prevention (PEP) trial clearly demonstrates that patients with hip fracture receiving stockings plus aspirin had a significantly lower risk of symptomatic VTE than patients receiving aspirin alone.[55]

Novel antithrombotic agents

Despite the use of methods considered to be effective, there is a high VTE prevalence in certain high risk patient populations. New direct thrombin inhibitors such as recombinant hirudin (desirudin) have been introduced recently. Ericksson and associates have documented better results with hirudin (15 mg BID) than with UFH[151] with low molecuar weight (40 mg OD) in total hip replacement patients.[152] These investigators identified that advanced age, general anesthesia, obesity, and the use of cemented prostheses were statistically associated with a higher risk of postoperative VTE. However, hirudin was more effective than enoxaparin after adjustment for these prognostic factors. Other heparin-related antithrombotic agents under evaluation in a number of ongoing clinical trials are pentasaccharide, which inactivates factor Xa without anti-II activity, dermatan sulphate, heparin sulphate, and danaparoid.

Recommendations

Low-risk patients may receive either no specific prophylaxis or graduated compression stockings. Using IPC alone or with graduated compression stockings, or either LMWH or UFH depending upon the nature of their risk factors may be appropriate for moderate-risk individuals. The physical methods may be employed in these moderate-risk patients during laparoscopic surgery, while the pharmacologic agents may be more

VENOUS THROMBOEMBOLISM RISK ASSESSMENT MODEL FOR SURGICAL AND MEDICAL PATIENTS

STEP 1: EXPOSING RISK FACTORS ASSOCIATED WITH CLINICAL SETTING

Assign 1 factor	Assign 2 factors	Assign 3 factors	Assign 5 factors
☐ Minor surgery	☐ Major surgery* ☐ Immobilizing plaster cast ☐ Medical or surgical patients confined to bed >72 hours ☐ Central venous access	☐ Myocardial infarction ☐ Congestive heart ☐ failure ☐ Severe sepsis/infection	☐ Elective major lower ☐ extremity arthroplasty ☐ Hip, pelvis, or leg fracture ☐ Stroke ☐ Multiple trauma ☐ Acute spinal cord injury

*Operations where the dissection is important or last longer than 45 minutes, including laparoscopic procedures

BASELINE RISK FACTOR SCORE (If score = 5, go to step 4):

STEP 2: PREDISPOSING RISK FACTORS ASSOCIATED WITH PATIENT

PATIENT RISK FACTORS Assign 1 factor unless otherwise noted

CLINICAL SETTING	MOLECULAR INHERITED	ACQUIRED
☐ Age 40 to 60 years (1 factor) ☐ Age over 60 years (2 factors) ☐ History of DVT/PE (3 factors) ☐ Pregnancy or postpartum (<1 month) ☐ Malignancy (2 factors) ☐ Varicose veins ☐ Inflammatory bowel disease ☐ Obesity (>20% ideal body weight) ☐ Combined oral contraceptive/ hormonal replacement therapy	☐ Factor V Leiden/ Activated protein C resistance (3 factors) ☐ Antithrombin III deficiency (3 factors) ☐ Proteins C and S deficiency (3 factors) ☐ Dysfibrinogenemia (3 factors) ☐ Homocysteinemia (3 factors) ☐ 20210A prothrombin mutation (3 factors)	☐ Lupus anticoagulant (3 factors) ☐ Antiphospholipid antibodies (3 factors) ☐ Myeloproliferative disorders (3 factors) ☐ Disorders of plasminogen and plasmin activatio (3 factors) ☐ Heparin induced thrombocytopenia (3 factors) ☐ Hyperviscosity syndromes (3 factors) ☐ Homocysteinemia (3 factors)

TOTAL ADDITIONAL PREDISPOSING RISK FACTORS SCORE:

STEP 3: TOTAL RISK FACTORS (EXPOSING + PREDISPOSING):

STEP 4: RECOMMENDED PROPHYLACTIC REGIMENS FOR EACH RISK GROUP

Low Risk (1 factor)	Moderate Risk (2 factors)	High Risk (3-4 factors)	est Risk (r more factors)
No specific measures Early ambulation	LDUH (q 12 h), LMWH, IPC, and GCS*	LDUH (q 8 h), LMWH, and IPC GCS*(+LDUH or LMWH)	H, oral anticoagulants, **(+LDUH or LMWH), *(+LDUH or LMWH) sted dose heparin

*Combining GCS with other prophylactic methods (LDUH, LMWH, or IPC) may give better protection; **Data shows benefit of plantar pneumatic compression in orthopedic total joint arthroplasty and leg trauma and can be used when IPC not feasible or tolerated.

Figure 3. Proposed risk factor assessment model for medical and surgical patients.

appropriate in those with inflammatory bowel disease or a history of myocardial infarction. Finally, in the highest risk subjects, combinations of these methods is appropriate, including either LMWH or warfarin in cases involving total joint replacement.[13,21,153]

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Zusammenfassung
Wirksame medikamentöse und physikalische Methoden zur Prophylaxe venöser Thromboembolien (VTE) stehen in breitem Umfang zur Verfügung. Immer noch entwickelt sich jedoch bei einem erheblichen Anteil der Patienten eine VTE, weil die prophylaktischen Möglichkeiten zurzeit zu wenig in Anspruch genommen werden oder – noch häufiger – weil die vorbeugenden Maßnahmen nicht dem Grad des Thromboserisikos angemessen sind. In epidemiologischen Studien konnten Gruppen von klinischen oder chirurgischen Patienten mit einem sehr hohen VTE-Risiko identifiziert werden. Bei den meisten dieser Patienten liegen mehrere Risikofaktoren vor, die sie besonders anfällig für die Entwicklung thromboembolischer Komplikationen machen. Zahlreiche Modelle zur Beurteilung des klinischen Risikos wurden erarbeitet, mit deren Hilfe sich das mögliche VTE-Risiko eines Patienten klassifizieren und je nach geschätztem Risiko der geeignete Prophylaxemodus auswählen lässt.
Aus den veröffentlichten Daten lässt sich schließen, dass die meisten Patienten durch die Anwendung niedermolekularer Heparine (LMWH) ausreichend vor VTE geschützt sind. Physikalische Verfahren zur Vorbeugung wie z.B. Kompressionsstrümpfe mit graduiertem Andruck und intermittierende pneumatische Kompression der Beine können bei Patienten mit mittlerem Risiko angezeigt sein, vor allem bei Vorliegen eines hohen Blutungsrisikos. Bei hohem VTE-Risiko ist an eine Erhöhung der LMWH-Dosis oder eine Kombination medikamentöser und physikalischer Methoden zu denken. Neuartige Antikoagulanzien wie die direkten Thrombininhibitoren oder Faktor-Xa-Hemmer bieten möglicherweise einen verbesserten Schutz für Patienten, bei denen trotz Anwendung der momentan verfügbaren Prophylaxe noch ein Risiko verbleibt.

Sommario
Sono ampiamente disponibili metodi farmacologici e fisici efficaci per la prevenzione del tromboembolismo venoso (VTE). Eppure, una significativa parte di pazienti sviluppa un VTE perché la profilassi è generalmente troppo poco utilizzata, o, più frequentemente, perché l'intensità della profilassi non è adeguata rispetto al livello del rischio trombotico. A questo proposito, studi epidemiologici hanno identificato gruppi di pazienti in cura medica o chirurgica ad altissimo rischio di sviluppare un VTE. La maggior parte di questi pazienti presenta diversi fattori di rischio che la rendono incline a sviluppare complicazioni tromboemboliche. E' stato progettato un certo numero di modelli di valutazione del rischio clinico in modo da stimare il rischio potenziale di VTE di un paziente e selezionare la profilassi più appropriata, conformemente al rischio stimato.
In base all'evidenza disponibile grazie ai dati pubblicati, la maggior parte di pazienti in cura medica o chirurgica sarà adeguatamente protetta dal VTE tramite l'uso di eparine a basso peso molecolare (LMWHs). Le modalità meccaniche della profilassi, come le calze a compressione progressiva e la compressione pneumatica intermittente delle gambe, possono essere indicate nei pazienti a rischio moderato, particolarmente in quelli ad alto rischio di emorragia. Per i pazienti ad alto rischio, devono essere prese in considerazione dosi crescenti di LMWHs o una combinazione di metodi farmacologici e meccanici. I nuovi anticoagulanti, come gli inibitori diretti della trombina o gli inibitori del fattore Xa, possono offrire una migliore protezione per i pazienti che restano a rischio a dispetto dell'uso della profilassi normalmente disponibile.

Resumen
Se dispone ampliamente de métodos farmacológicos y físicos eficaces para prevenir el tromboembolismo venoso (TEV). Sin embargo, una proporción significativa de pacientes desarrollan TEV porque la profilaxis está infrautilizada o, con mayor frecuencia, porque la intensidad de la profilaxis no está adaptada al nivel del riesgo trombótico. A este respecto, estudios epidemiológicos han identificado grupos de pacientes médicos y quirúrgicos con un riesgo muy elevado de desarrollo de TEV. La mayoría de estos pacientes presentan varios factores de riesgo que les hacen especialmente susceptibles de desarrollar complicaciones tromboembólicas. Se han elaborado varios modelos de valoración del riesgo clínico para clasificar el riesgo potencial de TEV que presente un paciente y seleccionar la profilaxis más apropiada, en función del riesgo estimado. En base a la evidencia disponible a partir de los datos publicados, el uso de heparinas de bajo peso molecular (HBPM) aportará a la mayoría de pacientes médicos y quirúrgicos una protección adecuada. Podrían estar indicadas modalidades mecánicas de profilaxis, como medias de compresión graduada y compresión neumática intermitente de las extremidades inferiores, en pacientes con un riesgo moderado, sobre todo aquellos pacientes con un riesgo alto de hemorragias. En los pacientes de alto riesgo, cabría considerar dosis crecientes de HBPM o una combinación de métodos farmacológicos y mecánicos. Los anticoagulantes nuevos, como los inhibidores directos de la trombina o los inhibidores del factor Xa, pueden ofrecer una protección mejorada a los pacientes que siguen presentando un riesgo de TEV, a pesar de utilizar la profilaxis disponible actualmente.

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