Prevention of postoperative venous thromboembolism. Risk assessment and methods of prophylaxis

[La prévention de la thromboembolie veineuse postopératoire. Évaluation du risque et méthodes de prophylaxie]

Serge Motte MD PhD,* Charles Marc Samama MD PhD,† Joanne Guay MD FRCPC,‡ Jeanne Barré MD,§ Jeanne-Yvonne Borg MD,¶ Nadia Rosencher MD‖

Purpose: To describe risk assessment models that have been developed to stratify patients into different risk levels of postoperative venous thromboembolism (VTE) and then to review the different methods of prophylaxis and to outline the evidence supporting their effectiveness and safety.

Source: Our review of the literature is focused on consensus documents, recent large randomized trials and meta-analyses.

Principal findings: The risk of VTE is determined by the type of surgery and underlying patient factors. Risk assessment models are useful in stratifying patients into different VTE risk levels. However, multiple risk factors are often present in the same patient and in practice the evaluation of their relative contribution to the overall risk remains difficult. A variety of prophylactic strategies including physical and pharmacological methods have been shown to be effective in different patient groups. Patients with a moderate or high risk of VTE should receive prophylaxis consisting of an antithrombotic agent, unless contraindicated, used alone or in combination with a mechanical method. Recommendations concerning which prophylaxis to use and how intensive it should be are based mainly on data from trials using surrogate endpoints, and do not translate easily into practical decisions aiming to reduce the incidence of symptomatic events.

Conclusion: Although risk assessment models and recommendations provided by consensus documents are of practical assistance, a decision concerning any patient is best made by combining recommendations of the literature with clinical judgment, including individual patient risk factors for thrombosis and bleeding.

***Objectif** : Décrire les modèles d'évaluation du risque développés pour classer les patients selon différents niveaux de risque de thromboembolie veineuse postopératoire (TEV) et ensuite, revoir les méthodes de prophylaxie et ébaucher la preuve de leur efficacité et de leur sécurité.*

***Source** : Notre revue de la littérature est centrée sur des documents de consensus, de récentes grandes études randomisées et méta-analyses.*

***Constatations principales** : Le risque de TEV dépend du type de chirurgie et de facteurs sous-jacents reliés au patient. Les modèles d'évaluation du risque sont utiles pour classer les patients selon différents niveaux de risque de TEV. Cependant, de multiples facteurs de risque sont souvent présents chez le même patient et, en pratique, l'évaluation de leur contribution relative au risque global demeure difficile. Diverses stratégies prophylactiques, dont des méthodes physiques et pharmacologiques, se sont révélées efficaces auprès de différents groupes de patients. Les patients à risque modéré ou élevé de TEV devraient recevoir une thérapie préventive avec des antithrombotiques, à moins de contre-indication, utilisés seuls ou en combinaison avec une méthode mécanique. Les recommandations sur le choix de la prophylaxie à utiliser et sur son importance sont fondées principalement sur les données d'essais qui utilisent des paramètres indirects et ne se traduisent pas facilement en décisions pratiques visant à réduire l'incidence d'événements symptomatiques.*

***Conclusion** : Même si les modèles d'évaluation du risque et les recommandations fournies par les documents de consensus sont pratiques, toute décision concernant un patient est plus juste si on combine recommandations de la littérature et jugement clinique, comprenant les facteurs de risque individuels de thrombose et d'hémorragie.*

From the Service de Pathologie Vasculaire,* Cliniques Universitaires de Bruxelles, Hôpital Erasme, Université Libre de Bruxelles, Belgique; Département d'Anesthésie-Réanimation,† Centre Hospitalier Universitaire Avicenne, Assistance Publique Hôpitaux de Paris, Bobigny, France; Département d'Anesthésie-Réanimation,‡ Centre Hospitalier Universitaire Maisonneuve-Rosemont, Montreal, Quebec, Canada; Département d'Anesthésie Réanimation,§ Centre Hospitalier Universitaire Robert Debré, Reims, France; Unité Fonctionnelle d'Hémostase,¶ Centre Hospitalier Universitaire Charles Nicolle, Rouen, France; and the Département d'Anesthésie-Réanimation,‖ Centre Hospitalier Universitaire Cochin, Paris, France.

Address correspondence to: Dr. Serge Motte, Cliniques Universitaires de Bruxelles, Hôpital Erasme, Université Libre de Bruxelles, Route de Lennik 808, B-1070 Bruxelles, Belgique, Phone: 00 32 2 5554292; Fax: 00 32 2 5553536; E-mail: smotte@ulb.ac.be

DEEP vein thrombosis (DVT) and pulmonary embolism (PE) are two manifestations of the same disease called venous thromboembolism (VTE). Venous thromboembolism is a common complication of surgery and the need for appropriate thromboprophylaxis in different surgical settings is increasingly accepted. A variety of prophylactic strategies including physical and pharmacological methods have been shown to be effective in preventing postoperative VTE in different patient groups. It has been established that prophylaxis needs to be tailored according to the risk of VTE in order to optimize clinical benefits and cost-effectiveness.

This article focuses on the assessment of the risk of postoperative VTE and reviews the various methods of prophylaxis.

Assessment of VTE risk level

The risk of VTE is determined by the current clinical setting (exposing risk or situation-related risk) and underlying patient factors (predisposing risk or patient-related risk) which include clinical risk factors and biochemical disorders that lead to thrombophilia.[1] Thus, the situation-related risk is applied in addition to the patient-related risk to give an overall risk level. Individual risk assessment is therefore necessary to categorize patients, as additional patient risk factors may increase the risk of VTE when undergoing certain surgical procedures.

The situation-related risk

The incidence of DVT after surgery is affected by factors related to the surgical procedure itself including the type and site of surgery, the duration of the procedure, the type of anesthetic and the degree of postoperative immobilization.

Pooled analyses of events observed in control patients included in randomized trials evaluating methods of prophylaxis can give an idea of the level of VTE risk in different types of surgery.[2] However, the trials included in such analyses extend over a broad period of time and changes in the management of patients including more rapid mobilization and other advances in perioperative care that occurred during this period of time may have influenced the rate of VTE.[3]

General and gynecologic surgery

Based on the results of routine screening by contrast venography, the mean incidence of total DVT in general surgery patients included in randomized trials and not receiving prophylaxis was 19%. Seven percent of these thrombi involved proximal deep veins.[2] The frequencies of clinically overt PE and fatal PE were 1.6 and 0.9% respectively.[2] Patients who underwent general surgery for cancer were at higher risk with an average rate of DVT in untreated patients of 29%.

In gynecologic surgery, the mean incidence of DVT was comparable to that associated with general surgery. However, the reported frequency of DVT varied largely from 4 to 38% in 19 studies using routine fibrinogen uptake as the primary outcome.[2] Factors increasing the incidence of VTE included surgery for cancer and abdominal *vs* vaginal procedures.

Orthopedic surgery

In the absence of prophylaxis, the incidence of venographically-detected DVT after total hip replacement (THR) in patients included in prospective clinical trials published since 1980 ranged from 42 to 57%, with a proximal DVT rate of 18 to 36%.[3] The incidence of fatal PE is less certain and varied between 0.1 and 2.0%. The rates of total and proximal venographic DVT were similar after hip fracture surgery. However, fatal PE was more common than after elective arthroplasty. The reported frequency of postoperative fatal PE varied between 2.5 and 7.5%.[3] Factors increasing the incidence of VTE in hip fracture patients included advanced age and delayed surgery.[3] After total knee replacement (TKR), the incidence of total DVT and proximal DVT were 41 to 85% and 5 to 22% respectively. The rate of fatal PE varied between 0.1 and 1.7%.[3]

Neurosurgery

Venographic studies have demonstrated an incidence of DVT ranging from 24 to 33% in patients using elastic stockings (ES); approximately 5% of these thrombi involved the proximal veins.[4,5] In a recent study using a large administrative database, White *et al.* showed that the incidence of symptomatic VTE within three months after invasive neurosurgical procedures was 2 to 3%, a rate that was comparable to that observed after other types of surgery considered at high risk of VTE such as THR.[6] Risk factors that increase DVT rates include intracranial *vs* spinal surgery, malignant *vs* benign tumours, duration of surgery and leg weakness.

Patient-related risk

Patient-related risk factors that affect the incidence of postoperative VTE include increasing age, obesity, cancer and its treatment, previous VTE, oral contraceptives and hormone replacement therapy.[1] Various medical illnesses known to predispose to VTE such as heart failure (New York Heart Association class III or IV) or infection may also affect the risk of

TABLE I Risk assessment model Assistance Publique-Hôpitaux de Paris

Risk associated with the surgical procedure	*Risk level*	*Risk associated with the patient*
- Cholecystectomy - Arthroscopy - Neck surgery	1	- No risk factors
- Leg injuries managed with plaster casts - Complicated appendectomy - Spinal surgery in the absence of leg weakness - Hysterectomy - Surgery for Crohn's disease	2	- Age > 40 yr - Contraceptive medication - Varicose veins, obesity - Bed confinement > 4 days - Preoperative infection - Postpartum
- Surgery for cancer - Radical prostatectomy - Hip, pelvis, leg surgery - Spinal surgery in the presence of leg weakness	3	- Actual/developing cancer - Previous VTE - Lower limb paralysis - Thrombophilia

VTE = venous thromboembolism.

TABLE II Overall risk of VTE according to surgical- and patient-related factors

Risk associated with the surgical procedure	*Risk associated with the patient*	*Overall risk of VTE*
1	1	Low
	2	Moderate
	3	
2	1	
	2	
	3	
3	1	High
	2	
	3	

VTE = venous thromboembolism.

postoperative VTE. These predisposing factors are often present in combination and the risk of developing DVT increases in proportion to their number.[7] Thrombophilic disorders may also increase the risk of postoperative VTE. The more common thrombophilic abnormalities include resistance to activated protein C (factor V Leiden), prothrombin variant 20210A, antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody) and deficiency of antithrombin, protein C or protein S. The role of these thrombophilic abnormalities in the development of postoperative VTE has not yet been clarified.

Assessment of the overall risk of VTE

Risk assessment models have been developed to allow a more accurate stratification of patients according to their overall VTE risk. The experts of the American College of Chest Physicians stratify patients into four categories: low, moderate, high, and highest risk.[3] Risk levels have been defined on the basis of data provided by epidemiologic studies, rates of DVT among untreated or placebo-treated patients in trials and experts' opinion. This classification method takes into account different types of surgery and patient-related risk factors and provides an overall degree of risk useful to guide recommendations for prophylaxis. The classification includes a fourth risk category whereas most of the prophylaxis recommendations in Europe are based on three degrees of risk: low, moderate or high.[8] Although a fourth level should allow prophylaxis to be better tailored according to the risk of VTE, it is not clear in practice that each risk level will receive a different regimen, in particular in Europe where low-molecular-weight heparins (LMWH) are largely used.[9] However, with the development of new drugs, it is possible that better identification of higher risk patients could improve the benefit/risk and cost ratio of these new drugs.

A comprehensive risk assessment model has been developed by the Assistance Publique-Hôpitaux de Paris.[10] Patients undergoing different types of surgery are stratified separately (Table I). Specific patient-related risk factors are listed explicitly. Separate scores are assigned for risk due to surgery and for risk associated with patients. The overall thromboembolic risk is obtained from a chart by combining the two risk scores (Table II). This model attempts to quantify the contribution of different patient-related factors to overall risk. For example, a history of VTE or cancer is assigned a higher score than obesity or varicose veins.

The choice of method of prophylaxis is largely driven by the overall VTE risk and the risk of bleeding. Patients with a moderate or high risk of VTE should receive prophylaxis consisting of an antithrombotic agent, unless contraindicated, used alone or in combination with a mechanical method.[11] Prophylaxis is not required for patients with a low risk of VTE.

Continuing debate concerning risk levels

Are systematically detected DVT in asymptomatic patients appropriate to estimate risk levels?

The estimation of risk levels in different types of surgery is based mainly on the overall incidence of events observed in control patients included in randomized trials evaluating methods of prophylaxis. But in most trials, the primary outcome is a surrogate endpoint (e.g., routine venography) and the great majority of reported events are systematically detected DVT in asymptomatic patients, i.e., not clinical events.

Although there is some correlation between surrogate endpoints in trials and clinical outcome, the clinical relevance of systematically detected DVT in asymptomatic patients remains doubtful. Actually, the majority of thrombi detected by sensitive screening methods for DVT resolve spontaneously without causing symptoms. The incidence of asymptomatic DVT detected by these methods tends, therefore, to overestimate risk levels of VTE. It appears that the incidence of major clinical events after surgery reported in recent studies is, nowadays, acceptably low. For example, the six-month cumulative incidence of all symptomatic VTE and fatal PE was 3.4 and 0.3% respectively in a cohort of 1,162 consecutive THR patients for whom routine prophylaxis included ES and early mobilization.[12] Only 10% of these patients considered at high risk of VTE had received a pharmacological prophylaxis. Other recent studies of patients undergoing THR or TKR who received seven to ten days LMWH or warfarin report a three-month cumulative incidence of symptomatic non-fatal VTE events and fatal PE of about 3 and 0.1% respectively, despite an expected 25% prevalence of asymptomatic DVT at the time of hospital discharge.[13–17]

Are risk assessment models accurate?

Risk assessment models are of practical assistance in stratifying patients and provide useful guidance for physicians. However, multiple risk factors are often present in the same patient. These factors have a cumulative effect on the overall risk and in practice the evaluation of the relative contribution of each one to the overall risk remains difficult. Moreover, new thrombophilic disorders are continually being added to the list and, in the future, models including these new risk factors should be validated in order to more accurately identify patients at increased risk of postoperative VTE.

Prophylaxis of VTE

Mechanical methods

Since most trials evaluating mechanical methods of prophylaxis have not been able to blind the mechanical devices, their results should be interpreted with caution. Mechanical methods may not perform as well in routine clinical practice as in a trial because of relatively poor compliance with these methods. Some patients cannot effectively wear ES because of unusual limb size or shape.

Graduated compression stockings

A recent review of randomized controlled trials concerning general surgery patients showed that ES reduced the overall incidence of DVT from 19% in the control group to 7% in the treatment group.[18] However, evidence of the value of ES in preventing proximal DVT and PE is inconclusive because too few data are available. In patients undergoing THR or TKR surgery, small studies have shown that ES have little effect on the incidence of proximal DVT.[2] In neurosurgery patients, ES alone have been reported to be effective in reducing the prevalence of DVT determined by fibrinogen leg scanning in one trial, but two recent studies using routine venography show that the combination of ES with LMWH started postoperatively was more effective in reducing DVT rate than ES alone.[4,5]

In practice, stockings are often combined with pharmacological agents although data from clinical trials are scarce.[11,18] The combination of the two is expected to lead to better protection because both methods act on different physiopathologic mechanisms of thrombosis. They may be used as a sole prophylactic agent in patients at low risk of DVT. They may also be used alone in situations where pharmacological prophylaxis is contraindicated. They may be potentially valuable in reducing the risk of VTE after discharge from hospital in patients with poor mobility. However, the benefit of continued use of stockings following discharge should be evaluated by a randomized controlled trial. Limited evidence is available to distinguish between the benefits of knee- and thigh-length stockings. In a recent randomized study, thigh-length stockings have been shown to be better than knee-length stockings at preventing DVT detected by routine duplex ultrasonography in high-risk patients undergoing various surgical procedures.[19]

Intermittent pneumatic compression

Intermittent pneumatic compression (IPC) has not been studied in general surgery as thoroughly as other methods. Small studies have demonstrated that IPC is effective in reducing the overall incidence of DVT. However, it has not been proven that IPC prevents proximal DVT or PE in these patients.[2]

As far as orthopedic surgery patients are concerned, the utility of IPC is limited. Small studies suggest that it is effective in reducing the overall incidence of DVT after TKR.[3] In THR patients, it has been shown to be less effective than anticoagulant-based prophylaxis for preventing proximal DVT.[20] In neurosurgery patients, IPC appears to be effective in lowering the rate of DVT with a reduction of 68% of the overall DVT rate detected by fibrinogen leg scanning.[3] In practice, IPC is used mainly for prophylaxis of DVT in patients undergoing elective neurosurgery, in particular in situ-

ations where pharmacological prophylaxis is contraindicated. It can be used with ES although there is no evidence from clinical trials that the combination of the two provides a better protection. In high risk patients, it can also be used in combination with ES and pharmacological prophylaxis. For example, Goldhaber *et al.* reported recently a low rate of asymptomatic DVT (9.3%, mostly isolated calf DVT) detected by routine ultrasonography in 150 patients undergoing craniotomy for brain tumour who received both ES and IPC plus LMWH or unfractionated heparin (UFH) started postoperatively.[21]

Plantar compression using foot pumps

These devices produce hemodynamic effects on the lower extremities similar to that of IPC and, like IPC, they also stimulate fibrinolytic activity. The published experience with plantar compression devices is limited. In one trial including 290 hip surgery patients and comparing the method with 40 mg enoxaparin, there was no statistically significant difference in the rate of venographic DVT.[22] In TKR surgery, it has been shown to be efficacious in preventing venographic DVT in two small studies,[23,24] but LMWH was more so in two other trials.[25,26] In a more recent study, neither method provided superior prophylaxis.[27] No trials have yet been done in general surgery patients. Further studies comparing venous foot pumps with standard regimens are needed.

Anticoagulants

Unfractionated heparin

Unfractionated heparin is a mixture of glycosaminoglycan molecules with a wide range of molecular weights that acts as an anticoagulant by binding to antithrombin and accelerating the rate at which it inhibits clotting factors, particularly thrombin and activated factor X. The interaction of UFH with antithrombin is mediated by a unique pentasaccharide sequence found on one third of the chains. Low dose UFH (5000 U) is administered subcutaneously every 12 or eight hours in patients with moderate or high risk, respectively. In a pooled analysis including trials in general surgery patients, low-dose UFH was associated with a significantly increased incidence of postoperative wound hematomas from 4.1% in the control group to 6.3% in the treatment group.[28] Unfractionated heparin can induce thrombocytopenia in about 3% of the patients.[29] Heparin-induced thrombocytopenia (HIT) is characterized by the formation of IgG antibodies that recognize the complex of heparin and platelet factor 4 and activate platelets. It usually begins five to ten days after starting heparin, and its most important complication is thrombosis that can involve veins or arteries. A detailed discussion of HIT is presented elsewhere in this supplement.

In general surgery, pooled data from randomized trials using fibrinogen leg scanning as the primary outcome show that low-dose UFH reduces the incidence of DVT from 25% to 8% compared with untreated controls.[2] Data from a meta-analysis show a reduction of fatal PE with UFH prophylaxis from 0.71% to 0.21%.[28] In THR or TKR surgery, a fixed-dose of UFH is less effective than LMWH. An adjusted-dose of UFH to maintain the activated partial thromboplastin time in the upper normal range has been shown to be safe and effective after THR, but this method appears to be impractical in daily practice.[2]

Low molecular weight heparins

Low molecular weight heparins are produced by enzymatic or chemical depolymerization of UFH to generate a mean molecular weight one third that of UFH. They inhibit thrombin to a much lesser extent than UFH since most LMWH molecules are too short to be able to complex simultaneously with both antithrombin and thrombin. However, these short chains inactivate factor Xa and each LMWH is characterized by the ratio of its antifactor Xa to antifactor IIa activity.[30] Although their mode of action is similar, various LMWH preparations are obtained by different methods and differ sufficiently from each other in their pharmacokinetic properties that they may not be interchangeable. Low molecular weight heparins have several advantages over UFH: they have a better bioavailability after *sc* injection at low doses, they have a longer half-life and can be given once daily, they have a more predictable and reproducible response principally because their non-specific binding to plasma proteins is markedly reduced, and they are less likely to cause HIT (0.1%). As they are cleared mainly by the renal route, their half-life is prolonged in patients with impaired renal function. Low molecular weight heparins have little effect on the activated partial thromboplastin time and an antifactor Xa assay is used to measure their activity.

A large number of trials in general surgery have shown that LMWH (administered once a day) are approximately as effective as UFH (5000 U subcutaneously two or three times daily) at reducing the rate of thrombosis detected by screening.[31] As far as the risk of bleeding is concerned, doses of LMWH in excess of 3,400 anti-Xa units daily produce more bleeding than low-dose UFH, whereas lower doses of LMWH are associated with less bleeding than UFH without loss of efficacy in moderate-risk patients.[31] In

TABLE III Low-molecular-weight heparins regimens for the prophylaxis of VTE

General surgery	*Recommended doses**	
Moderate risk	Dalteparin:	2500 IU, 2 hr before surgery and once daily after surgery
	Enoxaparin:	2000 IU, 2 hr before surgery and once daily after surgery
	Nadroparin:	3100 IU, 2 hr before surgery and once daily after surgery
	Tinzaparin:	2500 IU, 2 hr before surgery and once daily after surgery
High risk	Dalteparin:	5000 IU, 12 hr before surgery and once daily after surgery
	Enoxaparin:	4000 IU, 12 hr before surgery and once daily after surgery
	Reviparin:	4200 IU, 12 hr before surgery and once daily after surgery
	Tinzaparin:	3500 IU, 2 hr before surgery and once daily after surgery
Orthopedic surgery	Ardeparin:	50 IU·kg^{-1} twice daily started 12–24 hr after surgery
	Dalteparin:	5000 IU, 12 hr before surgery and once daily after surgery
	Enoxaparin:	4000 IU, 12 hr before surgery and once daily after surgery or 3000 IU twice daily started 12–24 hr after surgery
	Nadroparin:	40 IU·kg^{-1} started 12 hr before surgery, 12 hr after surgery and once daily after surgery for 3 days, then 60 IU·kg^{-1} once daily
	Reviparin:	4200 IU, 12 hr before surgery an once daily after surgery
	Tinzaparin:	4500 IU, 12 hr before surgery and once daily after surgery or 75 IU·kg^{-1} once daily, started 12–24 hr after surgery

IU = international unit; VTE = venous thromboembolism. * Doses are expressed in anti factor Xa IU.

orthopedic surgery, LMWH have been shown to be more effective than fixed low-dose UFH and at least as effective or superior to adjusted-dose UFH after THR.[3] Low molecular weight heparins also provide a safe and effective prophylaxis in TKR surgery and hip fracture surgery. In neurosurgery patients, two recent studies show that LMWH prophylaxis started postoperatively combined with ES is more effective than ES alone.[4,5] As far as safety is concerned in these patients, a pooled analysis of three studies including a total of 922 patients shows that prophylaxis with LMWH was associated with a non-statistically significant increase in major bleeding (2.2% *vs* 1.3% in the control group).[32] None of the bleeding events was fatal or required reintervention. It should be stressed that LMWH prophylaxis was started 18 to 24 hr postoperatively and patients considered at high risk of surgical-related bleeding were excluded.

Low molecular weight heparins are now widely used because they are more convenient to administer than low-dose UFH. The disadvantage of LMWH relative to UFH is that they are more expensive. Furthermore, special precautions are needed when they are used in the postoperative period since an increased incidence in epidural/spinal hematomas has been reported with their introduction as antithrombotic agents in clinical practice.[33,34] Several LMWH preparations are available and the recommended doses must be individualized for each drug (Table III).

Danaparoid sodium is a heparinoid related to LMWH consisting of a mixture of heparan sulfate (80% of the mixture), dermatan sulfate and chondroitin sulfate. Relative to conventional LMWH, it has a higher antifactor Xa to antifactor IIa activity ratio, a much longer half-life, and it can be used in patients with HIT. Danaparoid (750 anti-Xa IU *bid*) has been shown to be effective in preventing venographic DVT after THR surgery. However, due to its higher cost relative to other methods, its clinical use in prophylaxis is limited to patients with a history of HIT.

FONDAPARINUX

Fondaparinux is a synthetic analogue of the naturally occurring pentasaccharide sequence and, like UFH and LMWH acts as an anticoagulant by binding antithrombin. Fondaparinux catalyses factor Xa inhibition by antithrombin but has no effect on the rate of thrombin inactivation. Fondaparinux has excellent bioavailability after *sc* injection and is administered once a day.

In a meta-analysis of four trials including 7,344 patients undergoing hip replacement, major knee or hip fracture surgery, fondaparinux once daily, started 6 ± 2 hr postoperatively reduced the incidence of total VTE events from 13.7 to 6.8% compared with enoxaparin.[35] However, the result was mainly due to a decrease in asymptomatic DVT detected by venography and there was no statistically significant difference in the rate of symptomatic events. Although major bleeding occurred more frequently in the fondaparinux group (2.7 *vs* 1.7%, $P = 0.008$), the incidence of bleeding leading to death, re-operation or occurring in a critical organ did not differ between the two groups. Moreover, a post hoc analysis showed

that the rate of major bleeding when the first injection was given at least six hours after surgery was similar to that in the enoxaparin group. In another recent trial comparing extended duration fondaparinux for four weeks *vs* one week in patients undergoing hip fracture surgery, Eriksson *et al.* show that extended prophylaxis significantly reduced the risk of symptomatic VTE from 2.7 to 0.3% at four weeks.[36] However, there was a trend towards more major bleeding in the fondaparinux group (2.4 *vs* 0.6%, $P = 0.06$). Another possible problem of fondaparinux is its half-life of 17 hr that must be taken into account if regional anesthesia is planned. Treatment with fondaparinux should not preclude regional anesthesia, provided the first dose is administered according to the manufacturer's recommendations (i.e., six hours postoperatively). About 50% of all patients included in the studies had regional anesthesia and no bleeding complications related to the procedure were reported.[35,36] It should be stressed that patients were excluded if an indwelling, intrathecal or epidural catheter was planned during the treatment period, or in case of unusual difficulty in achieving epidural or spinal anesthesia. Fondaparinux was initiated 12 hr preoperatively if surgery was delayed but omission of the preoperative injection was recommended if regional anesthesia was planned. Further clinical data and cost-effectiveness analyses are required before its widespread use can be recommended in daily practice.

Oral vitamin K antagonists

Oral vitamin K antagonists (VKA; e.g., warfarin sodium) inhibit vitamin K-mediated posttranslational modification of factors II, VII, IX, and X resulting in reduced functional levels of these factors. The initial dose is given the evening prior to surgery or as soon as possible after surgery. However, the target international normalized ratio of the prothrombin time of 2.5 (range 2.0–3.0) is not, usually, reached before the third postoperative day when coagulation factor levels have fallen sufficiently. This delayed effect of oral anticoagulants may reduce the risk of bleeding in the immediate postoperative period compared to agents which have a rapid onset of action such as LMWH. However, in a recent meta-analysis of studies in orthopedic surgery, Mismetti *et al.* showed that there was no significant difference in the risk of major hemorrhage or wound hematoma between VKA and LMWH.[37] The advantages of VKA are their oral administration and low cost. Their disadvantage is that laboratory monitoring is required for appropriate dosing because of the narrow therapeutic window.

Several studies show that adjusted-dose warfarin treatment is a safe and effective prophylactic method after THR or TKR. Warfarin treatment administered only during hospitalization is less effective than LMWH for the prevention of DVT detected by screening, but no difference has been reported in terms of symptomatic events.[3,37] Oral anticoagulation may be an attractive method to extend prophylaxis beyond the hospital stay. Two recent controlled studies have assessed its potential benefit in this indication after hip surgery. Prandoni *et al.* have shown that extended warfarin treatment for four weeks beyond hospital discharge significantly reduces the incidence of late VTE without enhancing the incidence of bleeding compared with warfarin treatment administered only during hospitalization.[38] In the second trial reported by Samama *et al.*, the benefit-risk ratio of extended prophylaxis with oral anticoagulation was compared with that of extended LMWH prophylaxis.[39] This study showed that adjusted-dose acenocoumarol, a short-acting oral anticoagulant, was as effective as LMWH prophylaxis in preventing late symptomatic VTE events, but was associated with a significantly higher incidence of clinically serious bleeding (5.5 *vs* 1.4%). Further studies are needed to better assess clinical benefit-risk and cost ratio of extended treatment with the different oral anticoagulants available in comparison with LMWH.

Direct thrombin inhibitors

Direct thrombin inhibitors specifically bind to free and clot-bound thrombin and prevent its interaction with substrates. Hirudin has been shown to be highly effective in preventing VTE after hip surgery, but this molecule must be given intravenously and is expensive. Melagatran is a synthetic, low molecular weight, competitive thrombin inhibitor. It has a low oral bioavailability but its pro-drug, ximelagatran, can be given orally. The therapeutic window of this new agent is particularly wide; therefore no coagulation monitoring is required. Moreover, in comparison with oral VKA, food or alcohol do not interfere with this new agent and no clinically relevant drug interactions with drugs metabolized by the P450 pathway have been demonstrated.[40] Nevertheless, transient elevations in liver enzymes, particularly alanine aminotransferase more than three times the upper limit of normal have been observed in about 6.5% of patients with long-term use of ximelagatran. These elevations have mostly occurred between two and six months of treatment and have resolved either spontaneously or when treatment was discontinued.[41] Therefore, liver enzymes must be monitored after two months of treatment. However, ximelagatran is contraindicated in patients with liver impairment or preoperative ala-

nine aminotransferase values more than two times the upper limit of normal. Recent studies have evaluated different regimens of ximelagatran/melagatran in the prophylaxis of VTE after hip or knee surgery. In a study including patients undergoing THR and using as primary efficacy variable the composite endpoint of DVT (symptomatic or detected by routine venography) and/or PE, ximelagatran 24 mg twice-daily was less effective than enoxaparin 30 mg twice-daily, both regimens being initiated the morning after surgery.[42] Subcutaneous melagatran started four to 12 hr postoperatively, followed by oral ximelagatran twice-daily tended to be less effective than enoxaparin started 12 hr after THR or TKR regarding the composite primary endpoint defined as DVT detected by venography, PE or unexplained death (31 *vs* 27.3%, $P = 0.053$).[43] However, the rate of major VTE (venographic and/or symptomatic proximal DVT, fatal and non-fatal PE and unexplained death) was comparable (5.7 *vs* 6.2% in the ximelagatran and the enoxaparin group respectively). In this study the rate of major bleeding was comparable between the two groups, although the incidence of transfusion was significantly lower in ximelagatran-treated patients (62 *vs* 66%).[43] In another study in major elective orthopedic surgery, *sc* melagatran 2 mg was started at the beginning of surgery, followed by 3 mg after surgery and thereafter by oral ximelagatran 24 mg twice daily from the day after surgery.[44] This regimen was more effective than enoxaparin regarding major VTE defined as venographic and/or symptomatic proximal DVT, PE and/or death where PE could not be excluded (2.3 *vs* 6.3%) but was associated with excessive bleeding as assessed by the surgeon at operation. Ximelagatran has been compared with warfarin in two studies including patients undergoing TKR surgery. In one study, seven to 12 days of fixed-dose ximelagatran 24 mg twice daily was at least as effective as warfarin, both regimens being initiated the morning after TKR.[45] In the second study, ximelagatran at a dose of 36 mg twice-daily for seven to 12 days was more effective than warfarin regarding the primary composite endpoint defined as total DVT, PE and death from all causes (20.3 *vs* 27.6%). Rates of bleeding were similar between the two groups.[46] Ximelagatran/melagatran appears promising in the prevention of VTE, but further studies are needed to establish the safety of extended prophylaxis in fragile patients.

Aspirin

A pooled analysis of randomized trials suggests that aspirin is somewhat effective in preventing VTE.[2] However, it appears to be less effective than other agents and causes a small increase in bleeding. In a recent large trial including 13,356 patients undergoing hip fracture surgery, aspirin 160 mg significantly reduced the rate of fatal PE and of DVT compared with placebo.[47] However, the clinical benefit was balanced by an increase in cardiac events and major bleeding. Consequently, aspirin is not recommended for primary prophylaxis.[3]

Continuing debate concerning prophylactic regimens

Timing of the first dose in orthopedic surgery

As the surgical procedure is believed to be the initiator of the thrombotic process, in Europe prophylaxis is started 12 hr before surgery. But because of concerns about bleeding during surgery and inference with regional anesthesia, in North America prophylactic regimens are started 12 to 24 hr after the operation. There are no large convincing clinical trials comparing these two strategies directly. In a recent meta-analysis, there was no evidence that initiating prophylaxis before surgery was more effective in preventing venographic DVT than starting after, and that a postoperative regimen was safer than the preoperative regimen.[48] A third strategy is to start shortly before or after surgery with adapted doses. Relative to the two other strategies, this perioperative approach may lower the incidence of postoperative DVT but it is associated with an increase in the risk of major bleeding and, at least in the case of LMWH prophylaxis, this regimen would preclude concomitant neuraxial blockade.

Duration of prophylaxis

The presence of residual asymptomatic thrombi detected by screening in patients who receive short-duration prophylaxis has led to consideration of extended prophylaxis for several weeks after hospital discharge. This approach makes sense, particularly in patients undergoing THR since White *et al.* have shown that the diagnosis of symptomatic VTE in these patients was made after hospital discharge in 76% of cases, with a median time of diagnosis of 17 days after arthroplasty.[49] Several randomized studies of patients undergoing THR have shown that extended LMWH prophylaxis for four to six weeks after hospital discharge decreases the incidence of venographically detected DVT by at least 50%.[50–54] These trials, taken individually were too small to demonstrate a significant reduction of symptomatic events. However, three meta-analyses show that extended prophylaxis reduced the incidence of symptomatic events in parallel with the reduction of the incidence of venographic DVT.[55–57] However, since most DVT that develop despite a short course

of prophylaxis resolve spontaneously without causing symptoms, the incidence of symptomatic events is low and the need for prolonged prophylaxis after discharge for all patients is questioned by some experts.[3,17] There is also some uncertainty concerning the cost-effectiveness of universal prolonged prophylaxis since the incidence of symptomatic events is low. More intense and prolonged prophylaxis should therefore be administered to patients in whom an asymptomatic thrombus is prone to propagate and to become symptomatic. In practice, all patients should receive at least seven to ten days of prophylaxis. More prolonged prophylaxis for four weeks should be proposed for patients at increased risk (for example, those who are not fully weight bearing or who are immobilized, those with previous VTE or obesity).[3] As mentioned previously, the problem is that our ability to identify patients at high risk for symptomatic VTE is limited and further studies should determine the surgical and patient-related factors that predispose to the development of late symptomatic VTE after hip surgery.

As far as TKR is concerned, the high prevalence of residual asymptomatic thrombi detected by screening has led to a recommendation that the same duration of prophylaxis be applied as for hip surgery.[2] However, the rationale supporting this approach in patients undergoing knee surgery is not clearly established. Firstly, when patients undergoing THR and TKR are compared, the prevalence of asymptomatic thrombosis after seven to ten days of prophylaxis is more than twofold higher after TKR, but the incidence of symptomatic VTE is lower than after THR.[17] Secondly, the temporal pattern of symptomatic VTE after TKR or THR is different with an estimated median time of diagnosis after surgery of seven and 17 days respectively.[49] Thirdly, no study of patients undergoing TKR has shown that extended prophylaxis for four to six weeks after hospital discharge decreases the incidence of venographically detected or symptomatic DVT. In a recent study, prolonged prophylaxis with enoxaparin reduced the incidence of venographic DVT in patients undergoing THR but had not effect in those undergoing TKR.[58] Therefore, ten to 15 days of prophylaxis is probably appropriate for the great majority of patients undergoing TKR.

Conclusions

Several methods of prophylaxis have been shown to be safe and effective in preventing postoperative VTE. The evaluation of various risk factors allows the stratification of patients into risk categories which, in turn, will guide the choice and intensity of prophylaxis. The risk of developing VTE depends on risk factors associated with surgery and risk factors associated with the patient. The latter are often multiple in the same patient and their relative importance and possible cumulative effects are not yet fully known and understood.

Most trials on the prevention of VTE have used surrogate endpoints. Data provided by these trials are not easily translated into practical decisions in view of reducing the incidence of symptomatic events. The decision concerning any patient is best made by combining published recommendations with clinical judgment of individual patient risk factors for thrombosis and bleeding. Patients with a moderate or high risk of VTE should receive prophylaxis consisting of an antithrombotic agent, unless contraindicated, used alone or in combination with a mechanical method.

During the review process of this article, melagatran has been withdrawn from the market. The decision was made by the company because of a report of severe liver injury in a patient participating in a clinical trial.

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