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PREVENTION OF VENOUS THROMBOEMBOLISM IN HIGH RISK PATIENTS

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ABSTRACT

Background and Objective. Venous thromboembolism includes two closely related clinical manifestations: deep vein thrombosis (DVT), more commonly of the lower limbs, and pulmonary embolism. Pulmonary embolism is the most common cause of preventable death in hospitalized patients. The definition of the risk factors for venous thromboembolism should allow to adopt the most suitable prophylactic regimen. Determinants for the risk of venous thromboembolism are patient risk factors, both clinical and molecular, and the clinical setting. In this article the prophylactic regimens most widely employed in the prevention of venous thromboembolism in high-risk clinical settings will be reviewed. Then, the available guidelines for the management of thrombophilic patients will be given.

Information sources. The authors have been working in this field contributing original papers. In addition, the material examined in this review article includes papers published in the journals covered by the Science Citation Index® and Medline®.

State of art and Perspectives. Pharmacological prophylaxis is an effective approach for reducing morbidity and mortality from venous thromboembolism. Nevertheless, prophylaxis for venous thromboembolism is under employed because the incidence of venous thromboembolism is underestimated and there is fear of bleeding side effects. Adopting the proper prophylactic strategy for venous thromboembolism requires defining the patient risk factor. Determinants for the risk of venous thromboembolism are patient risk factors, both clinical and molecular, and the clinical setting. The risk connected with the clinical setting is the only risk defined by properly performed epidemiological studies. High-risk clinical settings are major orthopedic surgery, elective neurosurgery, spinal cord injury, cancer surgery and multiple trauma. The most effective anticoagulant regimens in the prevention of venous thromboembolism in high-risk patients are adjusted-dose unfractionated heparin, low molecular weight heparins (LMWHs) and oral anticoagulants. LMWHs are as effective and safe as the other two agents, but they do not require laboratory monitoring. On the other hand, LMWHs are more expensive than unfractionated heparin and warfarin. The use of effective agents still leaves the patients with a high prevalence of venous thromboembolism. Hence the search for more effective agents such as selective thrombin inhibitors like hirudin and its analogues. In patients undergoing elective hip surgery, hirudin has been recently shown to be more effective than low-dose unfractionated heparin and the LMWH enoxaparin.

Key words: venous thromboembolism, pulmonary embolism, heparin, LMWHs, warfarin, hirudin

Venous thromboembolism includes two closely related clinical manifestations: deep vein thrombosis (DVT), usually of the lower limbs, and pulmonary embolism.[1] Pulmonary embolism is the most common cause of preventable death in hospitalized patients. A recent overview estimated that 100,000 patients die of pulmonary embolism each year in the United States.[2] In most of the cases pulmonary emboli originate from asymptomatic deep vein thrombi. Several studies showed that screening high-risk patients with serial non-invasive testing is barely effective, due to the relatively low sensitivity of non-invasive diagnostic methods in asymptomatic patients.[3] Moreover, the policy of early treatment after the onset of clinically overt events, the so-called *wait and treat policy*, exposes patients to unacceptable risks. Indeed the first manifestation of venous thromboembolism might be represented by a massive pulmonary embolism, which is fatal in a large number of patients within the first 30 minutes from the onset of symptoms.[4] For these reasons, systematic pharmacological prophylaxis in patients at high risk for venous thromboembolism is the most effective approach for reducing morbidity and mortality from this pathology. In spite of this evidence, pharmacological pro-

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phylaxis is only adopted in about 30% of patients, as shown by a recent overview.[5] There are two reasons for the under utilization of pharmacological prophylaxis for venous thromboembolism: the unjustified feeling that the prevalence of venous thromboembolism is lower than what is reported in the literature and the overestimation of the incidence of bleeding complications. With regard to the first point, we must consider that the estimated prevalence of fatal pulmonary embolism in low-risk patients is about 0.5% without prophylaxis. This proportion increases to about 1.5% in patients undergoing elective hip surgery and rises to 4-7% in patients undergoing emergency hip-surgery.[6] As far as bleeding side effects are concerned, clinical studies have shown that prophylaxis with anticoagulants leads to a higher prevalence of surgically-related minor bleeding and wound hematomas,[7] but not to a statistically significant increase in major bleeding.[8] Finally, many studies showed that perioperative prevention of venous thromboembolism is highly cost-effective.

The definition of the risk factors for venous thromboembolism should allow us to adopt the most suitable prophylactic regimen. Determinants for the risk of venous thromboembolism are patient risk factors, both clinical and molecular, and the clinical setting. Patient clinical risk factors are mainly previous venous thromboembolism and cancer, followed by age over 70, bed rest for longer than 4 days and severe medical illness, such as recent stroke or myocardial infarction (see Table 1). Molecular risk factors can be subdivided into inherited and acquired. Among the inherited ones are antithrombin III, protein C or protein S deficiencies, activated protein C resistance and hyperhomocysteinemia, while the acquired factors include lupus anticoagulant and antiphospholipid syndrome. The risk connected with the clinical setting, mostly surgical settings, is the only risk defined by properly performed epidemiological studies. High-risk clinical settings are major orthopedic surgery, elective neurosurgery, spinal cord injury, cancer surgery and multiple trauma. The definition of the risk for perioperative venous thromboembolism is mainly based on clinical risk factors that are present before surgery. No reliable epidemiological data are available concerning congenital and acquired abnormalities of the hemostatic system, nor have clinical trials been performed on this specific population that has been excluded from most clinical trials. Furthermore, awareness of the presence of these abnormalities is after the fact in most cases. Assessment of individual risk for perioperative venous thromboembolism by laboratory testing has been an unachieved goal for a number of years. Prospective studies, including plasma assay of thrombin activity markers, have recently shown promising results.[9] These findings require further confirmations. Categorizing patients into different risk classes would allow us to adopt different prophylactic measures in different patients (see Table 2). Prophylactic methods can be classified into pharmacological agents that interfere with blood coagulation, such as heparin and warfarin, or with fibrin stability, such as dextran, and non-pharmacological methods that accelerate venous outflow, such as graduated compression elastic stockings (ES) or intermittent pneumatic compression (IPC). The most effective anticoagulant regimens in the prevention of venous thromboembolism in high-risk patients are adjusted-dose unfractionated heparin, low molecular weight heparins (LMWHs) and oral anticoagulants. Adjusted-dose unfractionated heparin is given three times daily by subcutaneous injection at a dose able to maintain the activated partial thromboplastin time (aPTT) in the upper limit of the normal range. Prophylaxis starts with a 3,500 U dose two hours before surgery.[10] Adjusted dose oral anticoagulants should be employed in a way as to maintain a targeted international normalized ratio (INR) of 2-3. There are two modalities for using oral anticoagulants in the prevention of postoperative DVT. The first is to

Table 1. Clinical risk factors for venous thromboembolism age > 60 years.

Extensive surgery
Previous venous thromboembolism
Marked immobility, preoperative or postoperative
Major (hip or knee) orthopedic surgery
Fracture of pelvis, femur or tibia
Surgery for malignant disease
Postoperative sepsis
Major medical illness (i.e. sepsis, myocardial infarction)

Table 2. Risk categories for venous thromboembolism.

Low-risk	*Moderate-risk*	*High-risk*
Patient < 40 yrs	General surgery in patient > 40 y	Major (hip or knee) orthopedic surgery
Uncomplicated surgery (i.e. hysterectomy)	Acute myocardial infarction	Previous venous thromboembolism
Minimal immobility	Chronic illness	Major trauma
	Leg fracture in a patient < 40 yrs	Elective neurosurgery
		Spinal cord injury
		Surgery for extensive for malignant disease

start oral anticoagulants pre-preoperatively and adjust the dose to obtain an INR of about 1.5 before surgery. The intensity of the anticoagulation is then increased (INR 2-3) in the postoperative period.[11] The alternative method is to start oral anticoagulants on the day before surgery or on the first postoperative day, in order to reach effective anticoagulation (INR 2.0 to 2.5) within 4 or 5 days.[12] Adjusted-dose unfractionated heparin or oral anticoagulants are effective and relatively safe but require accurate laboratory monitoring to minimize the risk of bleeding side effects. Thus, these regimens are rarely adopted and their cost-effectiveness has not even been established. LMWHs are derivatives of unfractionated heparin produced by its depolymerization. LMWHs are as effective and safe as the other two agents but they do not require laboratory monitoring. On the other hand, LMWHs are more expensive than unfractionated heparin and warfarin.

In this article, the prophylactic regimens most widely adopted in the prevention of venous thromboembolism in high-risk clinical settings will be reviewed. Then, the available guidelines for the management of thrombophilic patients will be given.

Prophylaxis of venous thromboembolism in major orthopedic surgery

Major orthopedic surgery is the high-risk clinical setting in which the prevention of postoperative venous thromboembolism has been most extensively studied.

Elective hip replacement

Patients undergoing elective hip replacement are at high risk for postoperative venous thromboembolism in spite of modern surgical techniques and early patient mobilization. Adopting spinal or epidural anesthesia whenever possible is helpful in reducing the prevalence of postoperative venous thromboembolism.[13] IPC and ES have been shown to be both effective and safe; however, their use is still associated with a unacceptably high risk of DVT, making pharmacological prophylaxis necessary.

A recent meta-analysis showed that aspirin is more effective than placebo in the prevention of DVT in elective hip surgery.[14] However, prophylaxis with aspirin has been found to be associated with a 56% prevalence of DVT in studies using venography to measure the endpoint. Thus, aspirin is not recommended for the prevention of venous thromboembolism in elective hip replacement. Subcutaneous fixed low-dose unfractionated heparin (LDUH), 5,000 U every 8-12 hours, has not been shown not to be here as effective as in general surgery and should not be adopted in major orthopedic surgery. Adjusted-dose unfractionated heparin, adjusted-dose oral anticoagulants and low molecular weight heparins (LMWHs) are more effective than LDUH in these patients (see Table 3). Two recent meta-analyses concluded that LMWHs are more effective than LDUH in patients undergoing elective hip replacement.[7,15] Several randomized trials showed that LMWHs are at least as safe and effective as adjusted-dose unfractionated heparin or oral anticoagulants in the prevention of venous thromboembolism in elective hip replacement.[16-18] The main advantages of LMWHs are that they do not need close laboratory monitoring and they are easy to administrate. For these reasons LMWHs are probably the agents of choice in the prevention of postoperative DVT in patients undergoing elective hip surgery. However, even when LMWH prophylaxis is utilized venous thromboembolism is still common. An extensive overview including data from 16 trials (2,571 patients) revealed a 15% prevalence of residual DVT (95% CI = 14-16%) among patients receiving LMWHs.[19] Hence there is a need for more effective anticoagulant agents. In this regard, selective thrombin inhibitors, hirudin and its analogues have recently been investigated. These agents are antithrombin III independent, act as bivalent inhibitors of thrombin and can inactivate clot-bound thrombin; for all these reasons they might surpass LMWHs in efficacy. Hirudin is a 65-amino acid peptide produced by the salivary glands of a medicinal leech (Hirudo medicinalis) now available through recombinant DNA technology.[20] Recombinant hirudin was tested in a dose-finding trial in patients undergoing elective hip surgery with promising results.[21] Then, several large randomized double-blind clinical trials were carried out. These trials compared recombinant hirudin versus LDUH, 5,000 U three times daily, and the LMWH enoxaparin. The results indicated that a twice daily 15 mg subcutaneous injection of recombinant hirudin is more effective than LDUH[22,23] and more effective than enoxaparin, 40 mg once a day, in the prevention of venous thromboembolism after elective hip replacement.[24] Moreover, these results are among the best ever reported with any prophylactic regimen in this clinical setting. Hirulog is a 20-amino acid synthetic analogue of hirudin that was investigated in a phase 2 dose finding study in patients undergoing major orthopedic surgery. The results showed that 1.0 mg/kg of hirulog given sub-

Table 3. Anticoagulant prophylaxis recommended in high-risk patients.

Low molecular weight heparins
Oral anticoagulants
Adjusted-dose heparin

cutaneously three times a day is effective and safe[25] while lower doses were not effective.

Elective knee replacement

Knee replacement surgery is characterized by high risk of postoperative DVT. Several trials have shown the efficacy of IPC in this clinical setting.[26,27] On the other hand, compression elastic stockings (ES) have proven to be scarcely effective in knee surgery patients.[28] The anticoagulant agents most commonly adopted are the same as those for patients undergoing elective hip surgery but the results are less satisfactory. Several trials compared LMWHs versus adjusted-dose warfarin in patients undergoing knee surgery. LMWHs were found to be more effective than oral anticoagulants; however, the prevalence of residual DVT was still high.[29-31] Moreover, some trials failed to demonstrate a reduction in the rate of proximal DVT in the LMWH group.[30,31] In conclusion, the prophylactic measures tested have not shown adequate efficacy in patients undergoing elective knee replacement.

Emergency hip surgery

The prevention of postoperative DVT in patients with hip fracture is quite problematic due to the advanced age of the majority of patients and the concomitant recent trauma. In spite of the risk of bleeding complications, there have been no well-conducted trials investigating non pharmacological prophylactic methods (IPC or ES). Antiplatelet prophylaxis shows very little efficacy in reducing the occurrence of postoperative venous thromboembolism. Two small trials conducted on hip fracture surgery patients revealed a 27% prevalence of DVT in patients treated with LDUH.[32,33] Similar results were obtained with LMWHs or low intensity oral anticoagulants (INR 1.2-1.5). Indeed the sample size of the LDUH trials (n=59) was quite small with a consequently wide confidence interval (17-38%). This evidence should be combined with the observed safety of lower intensity oral anticoagulants[34] and the stronger evidence about LMWH efficacy. Hence, the regimen of choice should be LMWHs or low intensity oral anticoagulants in adjunct to IPC or ES.

The optimal duration of prophylaxis in major orthopedic surgery patients

The optimal duration of prophylaxis after major orthopedic surgery is still unknown. Three randomized clinical trials conducted on patients undergoing elective hip replacement have recently been published. The results of these trials showed a marked reduction of venography detected DVT in patients having undergone one-month anticoagulant prophylaxis.[35-37] However, the large majority of these thrombi were asymptomatic and the clinical relevance of asymptomatic venography detected DVT is not clear. Our group reviewed patients having undergone major orthopedic surgery and found that those who had received pharmacological prophylaxis only during hospital stay (8-12 days) and were discharged with a negative venography displayed a negligible prevalence of clinically overt thromboembolic events (1.27%; 95% CI 0.82-1.72).[38] This is in keeping with the hypothesis that DVT develops during hospital stay and becomes symptomatic at home. A large-scale clinical trial having as an endpoint clinically overt venous thromboembolism, will define the safety and cost-effectiveness of one-month anticoagulant prophylaxis after hospital discharge.

Elective neurosurgery

The prophylaxis of choice in patients undergoing elective neurosurgery is still a matter of debate. Two main aspects have to be considered in this setting. First of all, the prevalence of DVT without prophylaxis is unacceptably high, ranging from 20 to 50%,[39] and fatal pulmonary embolism occurs in up to 1.5-5%.[40] On the other hand, it should also be kept in mind that fear of bleeding complications, in particular intracranial bleeding, characterizes this type of surgery. Hence, physical methods (IPC and ES) have been the ones most extensively investigated. IPC and ES have been shown to reduce postoperative DVT, but they have some limitations given that they are difficult to use and patient compliance is poor. Moreover, residual DVT are still common in spite of the adoption of these devices. Several clinical trials demonstrated that LDUH are effective both alone[41] and in combination with IPC.[42] Nevertheless, all these data are derived from trials lacking mandatory bilateral venography. A methodologically sound trial was carried out by Nurmohamed *et al*,[43] who compared the efficacy and safety of the LMWH nadroparin given postoperatively plus ES versus ES alone in patients undergoing elective neurosurgery. The results showed that nadroparin was associated with a decrease in the prevalence of overall DVT from 26.3% to 18.7% (relative risk reduction 28.9%). The difference was greater in terms of proximal DVT (11.5 and 6.9% respectively; relative risk reduction 40.2%). This finding has important clinical relevance, although a statistically significant difference was not observed. The use of nadroparin was associated with an increase in major bleeding (0.8% and 2.3%, respectively). In spite of the higher incidence of bleeding complications (none fatal), the risk/benefit ratio was still in favor of nadroparin. Further trials are required in order to establish the optimal prophylactic regimen.

Spinal cord injury

Patients with acute spinal cord injury are at high risk of venous thromboembolic complications; a

review reported 14.5% and 4.6% prevalence for clinically overt DVT and pulmonary embolism, respectively. The time of greatest risk seems to be during the first two weeks following the injury. Information concerning spinal cord injury is limited when compared with what is known about major orthopedic surgery. Moreover, these data are derived from small trials carried out without bilateral venography. In three of these trials LDUH was investigated; the control was placebo, adjusted dose heparin or the LMWH ardeparin.[44] An analysis of these results indicates that LDUH alone gives no adequate protection. The same consideration applies to IPC. LMWHs were investigated in preliminary trials with promising results.[44,45] Another confirmation of the efficacy of LMWHs comes from the trial conducted by Macoulliard *et al*.[46] which indicated that enoxaparin is more effective than adjusted-dose unfractionated heparin (aPTT within 10 seconds of the normal value) in reducing the rate of fatal pulmonary embolism. Large randomized trials are required to confirm these data.

Surgery in cancer patients

Reliable data on the prevalence of DVT in cancer patients and on the efficacy of pharmacological measures have become available only in recent years. Indeed most of the previous results had been extrapolated from clinical trials in which both cancer and non cancer patients were included. A recent review revealed a 29% prevalence of DVT detected by the fibrinogen uptake test in cancer patients undergoing general surgery in the absence of prophylaxis for venous thromboembolism.[19] In cancer patients undergoing general surgery, IPC has shown limited efficacy.[47] The most extensively studied anticoagulant agents have been LDUH (5,000 U every 8 or 12 hours)[48] and LMWHs. A comparison between LMWHs and LDUH was first made by Heilmann and colleagues in 261 patients undergoing abdominal, breast or vaginal surgery for gynecological malignancies.[49] These patients were randomized to receive a LMWH or LDUH (5,000 U three times daily). The results detected no significant differences in the rate of postoperative venous thromboembolism (7.6% and 9.2%, respectively) considered as DVT and/or pulmonary embolism. A slight increase in hemorrhagic complications was observed in the LDUH group. Further substantiation of the similar efficacy of LMWHs and LDUH in cancer patients comes from a large randomized trial by Bergqvist and colleagues,[50] who compared enoxaparin (40 mg once daily) versus LDUH (5,000 U three times daily) in patients having undergone curative abdominal or pelvic surgery for malignancy (n=1,115). Only 635 (56.5%) patients received adequate bilateral venography and were eligible for efficacy analysis. The prevalence of overall DVT was 14.7% in the enoxaparin group and 18.2% in the LDUH patients, respectively. This difference is not statistically significant. Moreover, there were no significant differences in bleeding side effects. These findings do not support the routine use of LMWHs in cancer patients since LMWHs have actually been shown to be only slightly better than LDUH (5,000 U) three times a day.

Multiple trauma

A prevalence of pulmonary embolism ranging from 2 to 22% has been reported in patients with major trauma, making it the third leading cause of death among these patients.[51] A large prospective study using venography revealed a 58% prevalence of overall DVT and an 18% rate of proximal DVT in 349 major trauma patients.[52] Advanced age, surgery, leg fractures, spinal cord injury and blood transfusions were associated with an increased risk of DVT.[52] These findings prompted a randomized venography clinical trial comparing LDUH (5,000 U twice daily) versus a LMWH (enoxaparin 30 mg twice daily).[53] Prophylaxis was started 36 hours after trauma and venography was performed at the 14th day. Treatment groups were well balanced with respect to demographics and injury characteristics. The results indicated an overall prevalence of DVT of 44.1% in patients randomized to LDUH and 31% in those receiving enoxaparin. The reduction in the overall prevalence of DVT was statistically significant (p=0.014) and the relative risk reduction was 30% (95% CI 4-50%). A greater decrease in the rate of proximal DVT was detected (14.7% and 6.2% respectively; p = 0.012), with a relative risk reduction of 58% (95% CI 12-87). A slight increase in major bleeding was observed in the enoxaparin group (2.9% and 0.6%, respectively), but none of these patients' hemoglobin fell by more than 2 gr/dL. This study confirms that patients with major trauma are at high risk for DVT. Furthermore, the prevalence of deep vein thrombosis observed with LMWHs is still too great to consider these agents as effective prophylaxis. Hence, the need for better anticoagulant agents for these patients deserves further research.

Molecular risk factors

The best known inherited molecular risk factors are antithrombin III, protein C and protein S deficiencies. Activated protein C resistance and hyperhomocysteinemia have been described more recently. There are no available data from randomized clinical trials on the prevention of postoperative thromboembolism in thrombophilic patients. Thus, existing guidelines are based on the results of small series of patients with antithrombin III, protein C or protein S deficiency. The limited data available demonstrate a substantial risk of postoperative

venous thromboembolism, making prophylaxis warranted in all patients. Thrombophilic patients should receive at least the optimal prophylactic measures currently adopted in non-thrombophilic patients. Transfusion therapy with plasma fractions should be considered as adjunctive prophylaxis in patients undergoing major orthopedic or cancer surgery, or following multiple trauma.[54] Indeed the risk/benefit ratio of these concentrates must be evaluated, weighing the potential risk of viral infection transmission. Other antithrombotic regimens like LMWHs or oral anticoagulants have not been investigated sufficiently in this group of patients. Hence, the need for further studies on thrombophilic patients is much greater than in other conditions.

The situation is even less clear as far as activated protein C resistance and hyperhomocysteinemia are concerned since these risk factors were discovered-more recently.[55,56] At present it is not possible to establish the optimal regimen of perioperative prophylaxis for venous thromboembolism in patients with antiphospolipid syndrome.

Conclusions

Although prophylaxis in patients at risk for venous thromboembolism can minimize mortality and morbidity from pulmonary embolism, it is still under-utilized. The definition of the risk of postoperative DVT on an individual basis should improve the efficacy of prophylaxis. Clinical and molecular risk factors are well known, but the classification of high-risk patients is still based on the presence of clinical risk factors combined with some well-defined high-risk clinical settings like major orthopedic surgery.

Recommended prophylactic agents vary in different clinical settings. In patients undergoing elective hip or knee surgery or in patients suffering major trauma the agents of choice are LMWHs, the alternatives being adjusted-dose unfractionated heparin or oral anticoagulants. In patients at higher risk of bleeding complications, e.g. emergency hip fracture or elective neurosurgery, or those at a relatively lower risk of DVT (surgery in cancer patients), data supporting the use of LMWHs are less clear. In these situations the prevention of venous thromboembolic complications should be accomplished by combining LDUH (5,000 U three times daily) with non-pharmacological measures (IPC or ES). Molecular risk factors are heterogeneous and rare, and the individual patient risk factor has not yet been determined. Thus, the existing guidelines for the prevention of postoperative DVT in thrombophilic patients are derived from small series of patients. Further studies are required to elucidate this situation. Finally, data are now emerging on the use of the pure thrombin inhibitor, recombinant hirudin, in the prevention of postoperative DVT in patients having undergone elective hip replacement.

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