

Prophylaxis of Venous Thromboembolism

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The recommendations on venous thromboprophylaxis have been updated on the basis of current evidence reviewed by a multidisciplinary team. The problem has been approached with regard to its relevance in both surgical and nonsurgical patients. It should be noted that these recommendations were drawn up for use in Spain and, therefore, should be implemented with the drugs and therapeutic practices authorized and generally accepted in this country.

Key words: Pulmonary embolism. Thromboembolism. Venous thromboembolism. Prevention. Prophylaxis. Preventative treatment.

Profilaxis de la enfermedad tromboembólica venosa

Un equipo multidisciplinario ha realizado una actualización de recomendaciones en la profilaxis de la enfermedad tromboembólica venosa basándose en las evidencias disponibles actualmente. Se ha abordado la problemática tanto del paciente médico como quirúrgico. Hay que puntualizar que esta Normativa está planteada para su utilización en el ámbito de España y, por lo tanto, debe aplicarse con los fármacos autorizados y las prácticas terapéuticas más aceptadas en este país.

Palabras claves: Embolia pulmonar. Tromboembolia. Trombosis venosa. Prevención. Profilaxis. Tratamiento preventivo.

1. Introduction

Venous thromboembolism (VTE), whether it takes the form of deep vein thrombosis or its most feared complication pulmonary embolism, represents a serious health problem owing to its repercussions in terms of morbidity, mortality, health care costs, and use of resources. The mortality rate associated with untreated pulmonary embolism is between 13% and 17%. Data supplied by the Spanish Ministry of Health and Consumer Affairs (Ministerio de Sanidad y Consumo) between 1999 and 2002 shows a gradual but constant increase in the number

of cases of VTE diagnosed.¹ The percentage of Spanish hospital admissions related to VTE has now almost reached 1%, and in-hospital mortality associated with this disease is now greater than 7%. This increase in incidence has been accompanied by a steady rise in health care costs. In 2002, the annual cost of hospital admissions associated with VTE was found to be €50 484 193.

In groups of patients with risk factors (Table 1), the best strategy is prevention of VTE by either mechanical preventive measures or pharmacological agents (Table 2). Prophylaxis for VTE is used when the expected benefits outweigh the risks involved. The following factors must be taken into account when deciding on the best prophylactic treatment for use in a specific case: the relevant evidence in the literature, knowledge of the patient's risk factors for VTE, the possibility of adverse events related to the prophylaxis, and the availability of different therapeutic options in each hospital or clinic.

These guidelines were drawn up to provide an update on the best scientific evidence available on the use of preventative measures for VTE in both medical and surgical patients and to summarize this evidence in a document that could serve as a useful reference in the clinical practice of respiratory medicine specialists, chest surgeons, and any general or specialist physician. The methods used to are summarized in Appendix 1.²⁻⁵

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2. Surgical Procedures and Conditions

In most of the randomized clinical trials involving surgical patients, preoperative prophylaxis was started 12 hours before surgery, the most common practice in Europe. However, a considerable number of authors have studied postoperative regimens, starting prophylaxis 12 hours after surgery, the commonly accepted practice in North America.² Reports are now emerging of a third regimen that involves administering the prophylactic agent closer in time to the intervention—2 hours before or 6 hours after surgery—based on the premise that a 12-hour interval is too long. While any of these options may be acceptable, when starting prophylaxis with a specific drug it is essential to base any therapeutic decisions on the clinical trials carried out with the drug to be prescribed and on the description of preoperative or postoperative use specified in the prescribing information sheet for that particular agent.

2.1 Risks Associated With Neuraxial Anesthesia and Analgesia

Although perispinal hematoma after a neuraxial block for anesthesia or analgesia is very rare, the incidence of this complication can be increased by the use of antithrombotic agents and the repercussions can be very serious.⁶ The US Food and Drug Administration (Public Health Advisory, 1997) stipulates that the pharmacokinetic profile of each agent must be taken into account when establishing optimum timing for epidural punctures.⁷ Catheter management in patients receiving low-molecular-weight heparin (LMWH) is dealt with in Spanish Ministry of Health circular number 20607-10/2001 dated October 11. The national society of anesthesiologists in Spain (Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor) has published guidelines on safe timing for neuroaxial anesthesia in patients receiving pharmacological prophylaxis (HBPM or fondaparinux).⁸ The basic recommendations are as follows:

1. In patients receiving preoperative LMWH, a minimum of 12 hours should elapse between the last dose of LMWH and neuroaxial puncture or the placement or withdrawal of a catheter. Similarly, after any of these procedures a minimum of 6 hours should elapse before a subsequent dose of LMWH is administered.

2. In patients receiving fondaparinux, no special precaution need be taken in the case of general anesthesia or single-puncture spinal anesthesia. In the case of catheters placed to facilitate administration of postoperative analgesia, at least 36 hours should elapse between the last dose of fondaparinux and catheter withdrawal (therefore skipping 1 dose of the drug). Likewise, at least 12 hours must elapse between catheter withdrawal and administration of the following dose.

2.1.1 Recommendations

– Mechanical prophylaxis should be used in cases where there is a high risk of hemorrhage (level A evidence) and

TABLE 1
Risk Factors for Venous Thromboembolism

Recent major surgery
Recent fracture or immobilization with a plaster cast of the lower limbs
Recent immobilization as a result of illness: New York Heart Association functional class III-IV heart failure, COPD exacerbations, sepsis, acute cerebral vascular accident
Congenital thrombophilia: antithrombin, protein C, or protein S deficit, homozygous or heterozygous Factor V Leiden mutation, combined deficits, homozygous factor II G20210A mutation, hyperhomocysteinemia, high plasma concentration of factor VIII, others
Prior history of venous thromboembolic disease, especially idiopathic
Cancer, especially with metastasis
Antiphospholipid syndrome
Advanced age
Pregnancy, puerperium
Obesity
Superficial venous thrombosis, varicose veins
Oral contraceptives, hormone replacement therapy, tamoxifen
Miscellaneous: polycythemia vera, thrombocytosis, paroxysmal nocturnal hemoglobinuria, nephrotic syndrome, inflammatory bowel disease, Behçet's syndrome, lupus erythematosus, antipsychotic medication

TABLE 2
Available Methods for the Prophylaxis of Venous Thromboembolism

Pharmacological Treatments
Low-molecular-weight heparins: bemiparin, dalteparin, enoxaparin, nadroparin, tinzaparin
Unfractionated heparin
Antivitamins K: acenocoumarol, warfarin
Indirect factor Xa inhibitors (fondaparinux)
Physical or nonpharmacological methods
Intermittent pneumatic compression
Graduated compression stockings
Venous foot pump

to complement pharmacological prophylaxis in patients at high risk for thrombosis (level B evidence). When physical methods are used, careful attention should be paid to ensuring patient compliance and correct use (level A evidence).

– Acetylsalicylic acid alone should not be used as a prophylactic measure (level A).

– Renal failure should be taken into account when deciding on the appropriate dose of LMWH, fondaparinux, direct thrombin inhibitors, or other antithrombotic agents, particularly in elderly patients and those at high risk for hemorrhage (level A).

– Extreme caution must be exercised when prescribing anticoagulant therapy to patients receiving neuraxial anesthesia or analgesia (A).

2.2 General Surgery

– In low-risk general surgery patients—that is, patients under 40 years old without additional risk factors undergoing a minor procedure (Table 3)—the use of

TABLE 3
Risk of Venous Thromboembolism (VTE) in Surgical Patients Not Receiving Prophylaxis^a

Levels of Risk	Procedures	Incidence Without Prophylaxis, %			
		Distal DVT	Proximal DVT	Clinical VTE	Fatal PE
Low	Minor surgery in patients <40 years of age with no additional risk factors	2	0.4	0.2	0.002
Moderate	Minor surgery with additional risk factors Minor surgery in patients aged 40-60 years Major surgery in patients aged <40 years with no additional risk factors	10-20	2-4	1-2	0.1-0.4
High	Minor surgery in patients >60 years of age Major surgery in patients >40 years Major surgery in patients with additional risk factors	20-40	4-8	2-4	0.4-1.0
Very high	Major surgery in patients >40 years of age who have a prior history of VTE, cancer, a hypercoagulable state, hip or knee fracture or arthroplasty, major trauma, or spinal cord injury	40-80	10-20	4-10	0.2-0.5

^aAdapted from three sources: *a*) Gallus AS, Salzman EW, Hirsh J. Prevention of VTE. In: Colman RW, Hirsh J, Marder VJ, editors. Haemostasis and thrombosis: basic principles and clinical practice, 3rd ed. Philadelphia: JB Lippincott; 1994. p. 1331-45; *b*) Nicolaidis AN, Berqvist D, Hull R. Prevention of VTE: international consensus statement. *Int Angiol*. 1997;16:3-38; and *c*) Geerts WH, Heit JA, Claret GP. Prevention of venous thromboembolism. *Chest*. 2001;119 Suppl:132-75. Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

prophylaxis (other than early and persistent mobilization alone) is not recommended (A).

– The moderate risk group comprises the following groups: patients undergoing a minor intervention who are aged between 40 and 60 years; patients undergoing a minor intervention who have at least 1 additional risk factor; and patients undergoing major surgery who are under 40 years and have no additional risk factors. Patients in this group should receive prophylaxis with LMWH at high-risk doses (Table 4) (A). Another alternative is low-dose unfractionated heparin (LDUFH) 5000 U twice daily (A).

– The high risk group comprises the following groups: patients undergoing minor procedures who are over 60 years of age and patients undergoing major surgery who have additional risk factors or are over 40 years of age. These patients should receive prophylaxis with LMWH at high-risk doses (Table 4) (A). Another alternative is LDUFH 5000 U 3 times a day (A).

– In patients with multiple risk factors undergoing high-risk general surgery, pharmacological prophylaxis should be complemented by physical preventive methods, such as graduated compression stockings (GCS) or intermittent pneumatic compression (IPC) (A).

– In patients undergoing general surgery who are at high risk for hemorrhage, mechanical prophylactic methods—GCS or IPC—should be used at least until the risk of hemorrhage has declined (A).

– In high-risk general surgery patients, such as cancer patients who have undergone tumor removal, continuation of prophylaxis is recommended for 2 to 3 weeks after discharge from hospital (B).

2.3 Vascular Surgery

– In patients undergoing vascular surgery who have no additional thromboembolic risk factors, routine prophylaxis is not recommended (A).

– Patients with additional thromboembolic risk factors undergoing major vascular surgery should receive prophylaxis with LMWH or LDUFH (A).

2.4 Gynecological Surgery

– In patients undergoing short gynecological surgical procedures (under 30 minutes) because of a benign disease, the use of prophylaxis (other than early and persistent mobilization alone) is not recommended (A).

– Patients undergoing laparoscopic surgery who have additional thromboembolic risk factors should be treated with 1 of the following types of prophylaxis: LMWH, LDUFH, IPC, or GCS (A).

– All patients undergoing major gynecological surgery should receive thromboprophylaxis (A).

– Patients without risk factors undergoing major gynecological surgery for a benign disease should be treated with LMWH at moderate-risk doses (Table 4) (A), LDUFH 5000 U twice daily (A), or IPC starting just before surgery and continuing until the patient is ambulatory (B).

– Patients undergoing extensive surgery for malignant neoplastic disease and patients with risk factors should routinely receive prophylaxis with LMWH at high-risk doses (Table 4) (A). Other acceptable treatment options in such cases are LDUFH 5000 U 3 times a day (A), IPC alone until discharge (A), or a combination of LMWH or LDUFH and mechanical prophylaxis with either GCS or IPC (B).

2.5 Urological Surgery

– In patients undergoing transurethral or other low-risk urological procedures, the use of prophylaxis (other than early and persistent mobilization alone) is not recommended (A).

– In patients undergoing major open urological surgery, prophylaxis with LMWH should be administered routinely (A). Alternatives in such cases are LDUFH 2 or 3 times a day (A), IPC (B), or GCS (B). In patients undergoing urological surgery who have active bleeding or a very high risk of hemorrhage, mechanical prophylaxis with GCS or IPC should be used, at least until the risk of bleeding has diminished (A).

– Patients with multiple risk factors should be treated with a combination of LMWH or LDUFH and mechanical prophylaxis with GCS or IPC (A).

2.6 Laparoscopic Surgery

– In patients undergoing laparoscopic surgery, the use of prophylaxis (other than intensive mobilization alone) is not recommended (A).

– Patients with thromboembolic risk factors should be treated with 1 or more of the following prophylactic measures: LMWH, LDUFH, IPC, or GCS (A).

2.7 Orthopedic Surgery

2.7.1 General Considerations

The use of oral anticoagulants—warfarin or acenocoumarol—as antithrombotic prophylactics in orthopedic surgery is a widespread practice in the United States, but very rare in Europe in general and specifically in Spain. These agents are not used because the onset of their action is delayed and patient response depends on diverse factors including concomitant medication, making close monitoring essential. Moreover, no randomized clinical trials have shown these oral anticoagulants to be better than other anticoagulant agents. In light of the above and the lack of training, clinical experience, and guidelines on the use of oral anticoagulants in Spain, we do not recommend routine use of these agents. The present guidelines do not, therefore, include recommendations for their use. However, in special cases when other available anticoagulants are contraindicated, these oral anticoagulants may be used (maintaining an international normalized ratio [INR] range of 2.0-3.0).

Direct thrombin inhibitors (melagatran-ximelagatran) have also been shown to be effective in antithrombotic prophylaxis. However, as these anticoagulants are not approved for use in Spain, the present guidelines do not include recommendations for their use.

Orthopedic surgery includes hip arthroplasty, knee arthroplasty, and hip fracture surgery. It has been reported that the incidence of deep vein thrombosis among patients who did not receive prophylaxis ranges from 40% to 60%, taking the form of proximal deep vein thrombosis in 10% to 30% of cases, and that between 3% and 28% of patients present pulmonary embolism on scintigraphic scans carried out during the 2 weeks following surgery.^{9,10} Prophylaxis is, therefore, used routinely in this type of surgery.

2.7.2 Recommendations

– In patients undergoing knee arthroplasty, one of the following regimens should be used: a) LMWH at a high-risk dose starting 12 hours before surgery, 12 to 24 hours after the intervention, or else 4 to 6 hours after surgery at half the high-risk dose followed by an increase to the full dose the following day (A); or b) fondaparinux at a dose of 2.5 mg/d starting 6 to 8 hours after surgery (A).

– The following prophylactic methods should not be used in isolation in patients undergoing hip arthroplasty:

TABLE 4
Dosage of Low-Molecular-Weight Heparin Stratified by Risk

	Dosage (U/d)	
	Low/Moderate Risk	High/Very High Risk
Dalteparin : Boxol, Fragmin	2500	5000
Nadroparin: Fraxiparin	2500	<70 kg: 3000 >70 kg: 4000
Bemiparin: Hibor	2500	3500
Enoxaparin: Clexane, Decipar	2000	4000
Tinzaparin: Innohep	3500	4500

Adapted from Navarro JL, García Avelló A, César JM. Heparinas de bajo peso molecular en la profilaxis de la enfermedad tromboembólica en pacientes quirúrgicos y médicos. In: Rocha E, Díaz S, Alegría A, editors. Heparinas de bajo peso molecular. Barcelona: Acción Médica; 2002.

TABLE 5
Absolute Risk of Deep Vein Thrombosis (DVT) in Hospitalized Patients^a

Patient Group	Prevalence of DVT, % ^b
Medical patients	10-20
General surgery	15-40
Major gynecological surgery	15-40
Major urological surgery	15-40
Neurosurgery	15-40
Cerebrovascular accident	20-50
Orthopedic surgery	40-60
Major trauma	40-80
Acute spinal cord injury	60-80
Critical care patients	10-80

^aAdapted from Geerts et al².

^bPercentages are based on objective diagnosis using imaging techniques in patients who did not receive thromboprophylaxis.

dextran, LDUFH, GCS, IPC, or venous foot pump (A).

– Patients undergoing knee arthroplasty should receive prophylaxis with LMWH or fondaparinux at a high-risk dose (A).

– Optimum use of IPC can be an alternative to anticoagulant prophylaxis in patients undergoing knee arthroplasty (B).

– Neither of the following methods should be used as the sole prophylactic measure in patients undergoing knee arthroplasty: LDUFH (A) or venous foot pump (B).

– Patients undergoing hip fracture surgery should routinely receive prophylaxis with fondaparinux (A), LMWH at a high-risk dose (A), or LDUFH (B).

– Mechanical prophylaxis should be used when anticoagulant therapy is contraindicated because of a high risk of bleeding (A).

– In orthopedic surgery, the decision about the best time to start pharmacological prophylaxis should be based on the balance between efficacy and risk of bleeding for each particular drug (A). In the case of LMWH, starting prophylactic treatment preoperatively or postoperatively are both acceptable options (A).

– Prophylaxis with LMWH at a high-risk dose or fondaparinux 2.5 mg/d should be continued for at least 10 days in patients who undergo hip or knee replacement or hip fracture surgery (A).

– After major orthopedic surgery, prophylactic treatment should be continued for up to 28 to 35 days if LMWH is

used (A) and up to 21 days in the case of treatment with fondaparinux (B).

2.7.3 Knee Arthroscopy

– In patients undergoing knee arthroscopy, the use of prophylaxis (other than early and persistent mobilization alone) is not recommended (C).

– Prophylaxis with LMWH is recommended in patients undergoing knee arthroscopy if the intervention is prolonged or the patient has risk factors (C).

2.7.4 Elective Spine Surgery

– In spine surgery patients with no additional risk factors, the use of prophylaxis (other than early and persistent mobilization alone) is not recommended (B).

– In patients with additional risk factors, some form of prophylaxis should be implemented (B). The options are postoperative LDUFH (A) alone; postoperative LMWH alone (B); perioperative IPC alone (B); perioperative GCS alone (C); or perioperative IPC combined with GCS (D). Patients with multiple risk factors for VTE should receive a combination of LMWH or LDUFH and mechanical prophylaxis with GCS or IPC (A).

2.8 Isolated Lower Limb Injuries

– Routine prophylaxis is not recommended in patients with isolated injuries of the lower limbs (B).

– Prophylaxis with LMWH should be used if the patient has additional risk factors for VTE (consensus).

2.9 Trauma

– All patients with traumatic injuries and at least 1 risk factor should receive prophylaxis (A).

– When not contraindicated, LMWH treatment should be started as soon as possible (B).

– If LMWH is contraindicated because the patient is actively bleeding or at high risk for hemorrhage, IPC or GCS should be used (B).

– Prophylaxis should be continued until the patient is discharged from hospital (A). After discharge, prophylaxis should be continued with LMWH or, when administration of LMWH would be difficult, with oral anticoagulants (INR range, 2.0-3.0) (D).

2.10 Acute Spinal Cord Injury

– Prophylaxis should be given to all patients with acute spinal cord injuries (A).

– LDUFH, GCS, and IPC should not be used as single prophylactic modalities (A).

– Prophylaxis with HBPM is recommended (B). The alternative is combined therapy with IPC and LDUFH (C).

– After an acute spinal cord injury, prophylaxis with LMWH should be continued during rehabilitation or the patient should be switched to an oral anticoagulant (INR range, 2.0-3.0) (B).

2.11 Burns

– Burn patients with additional risk factors should receive prophylaxis (A).

– If not contraindicated, LMWH or LDUFH should be used (A).

2.12 Neurosurgery

– Patients undergoing major neurosurgery should routinely receive prophylactic treatment (A).

– IPC, with or without GCS, should be used in patients undergoing intracranial neurosurgery (A). Acceptable alternatives are LDUFH (C) or postoperative LMWH (B).

– A combination of mechanical and pharmacological methods is recommended in patients at high risk for VTE (C).

3. Medical Conditions

3.1 General Considerations

Currently, 50% to 70% of symptomatic thrombotic events¹¹ and 70% to 80% of cases of fatal pulmonary embolism¹² occur in nonsurgical patients. Moreover, thromboembolic events in medical patients are associated with more severe complications in terms of recurrence, bleeding, and death from PE than those affecting surgical patients.¹³

Most of the research into risk factors for VTE among medical patients has investigated hospitalized patients. The chief risk factors identified were heart failure (New York Heart Association functional class III-IV), exacerbations of chronic obstructive pulmonary disease (COPD), sepsis, advanced age, prior history of VTE, cancer, acute cerebral vascular accident with paralysis of the lower limbs, and confinement to bed.^{15,16}

Several randomized controlled trials have demonstrated the greater efficacy of prophylaxis with LMWH or LDUFH compared to placebo.^{17,18} Prophylactic doses of LMWH in medical patients are similar to those used in surgical patients with moderate-to-high risk.¹⁴ Comparative studies have shown treatment with LMWH to be safer and as effective as LDUFH.¹⁹ Fondaparinux at a dose of 2.5 mg/d has been shown to be a more effective prophylaxis than placebo in medical patients.²⁰

The optimum duration of thromboprophylaxis in medical patients is not known. The results of the Extended Clinical Prophylaxis in Acutely Ill Medical Patients (EXCLAIM) clinical trial are likely to clarify some aspects of this question.²¹

3.2 General Recommendations

– Prophylaxis with LMWH at a high-risk dose should be administered to hospitalized medical patients who have congestive heart failure, severe respiratory disease, or who are confined to bed and present additional risk factors, such as cancer, a prior history of VTE, sepsis,

acute neurological disease, or inflammatory bowel disease (Table 4) (A). LDUFH is an acceptable alternative in such cases.

– When anticoagulation treatment is contraindicated in a medical patient at high risk for VTE, mechanical prophylactic measures—GCS or IPC—should be used (A).

3.3 Cancer Patients

– Hospitalized cancer patients confined to bed with an acute medical condition should receive prophylaxis (A).

– Cancer patients undergoing surgery should receive prophylaxis according to their risk evaluation as surgical patients (A).

– Prophylaxis with low doses of LMWH should not be used. (A).

– Routine use of prophylaxis for VTE in outpatients with cancer is not recommended (B).

– Prophylaxis with LMWH or warfarin is not recommended in cancer patients with central venous catheters because of the risk of catheter-associated thrombosis (C).

– Cancer patients not receiving chemotherapy should receive prophylaxis with LMWH if they are bedridden or have a combination of diseases or risk factors (consensus).

3.4 Acute Myocardial Infarction

Because current practice in the management of acute myocardial infarction calls for anticoagulant doses of thrombolytic agents and LMWH, it would make little sense to recommend prophylaxis with LMWH in the acute phase of myocardial infarction.

3.5 Heart Failure

– Patients hospitalized for congestive heart failure should receive prophylaxis with high doses of LMWH (Table 4) while they are bedridden (A). Fondaparinux 2.5 mg/d is an alternative option.

– Prophylaxis with low doses of LMWH should not be used (A).

– Routine prophylaxis is not justified in patients with congestive heart failure (B).

– In the case of patients who are not bedridden, LMWH should be administered to those over 60 years of age with 1 or more additional risk factor and to those under 60 years of age when there is an additional medical circumstance (consensus).

3.6 Unstable COPD

– Prophylaxis with LMWH should be administered to hospitalized patients with COPD while they are confined to bed (A). Fondaparinux 2.5 mg/d is an alternative option.

– Prophylaxis with low doses of LMWH should not be used (A).

– In patients for whom anticoagulation treatment is contraindicated, mechanical prophylactic measures—GCS or IPC—should be used (A).

3.7 Acute Infection

– Prophylaxis with LMWH at high doses should be administered to patients hospitalized for an acute infection while they are bedridden (A). Fondaparinux 2.5 mg/d is an alternative option.

– Prophylaxis with low doses of LMWH should not be used (A).

– In the case of patients who are not bedridden, LMWH should be administered to those over 60 years of age with 1 or more additional risk factor and to those under 60 years of age when there is an additional medical circumstance (consensus).

3.8 Cerebrovascular Accident and Consequent Paralysis of the Lower Limbs

– LMWH should be administered for 2 weeks in the acute phase of a cerebrovascular accident in patients at low risk for intracranial hemorrhage (A).

– All patients hospitalized for cerebrovascular accident should receive prophylaxis with LMWH until discharged from hospital (consensus).

– Prophylaxis with LMWH should be administered to patients with lower limb paralysis secondary to cerebrovascular accident when 1 or more additional risk factors are present (consensus).

3.9 Pregnancy and Puerperium

– Pregnant women at high risk for VTE should receive prophylaxis with LMWH at a high-risk dose (Table 4) (B).

– Pregnant women should receive prophylaxis with LMWH if they are confined to bed and have an additional risk factor, or if they present either 2 medical circumstances or a single medical circumstance and a risk factor for VTE (consensus).

– LMWH or physical preventative measures should be used in pregnant patients who are bedridden or obese but have no other risk factors and in nonobese pregnant women in the presence of a minor medical circumstance (consensus).

– In the case of pregnant women with thrombophilia and no history of VTE, a specialist consultation should be ordered to assess the risk in view of the diversity of different types of thrombophilia (consensus).

4. Long Distance Travel

Despite much controversy about the risk of VTE on long distance flights, the actual statistics found by 1 study were 1 pulmonary embolism per 700 000 passengers traveling for over 6 hours and 1 PE per 100 million passengers traveling for under 6 hours.²² It is interesting to note, however, that many of the people who have had VTE episodes during flights have later been identified as having 1 or more preexisting risk factors for thrombosis, and this finding makes it difficult to determine the real association between thrombotic events and long-haul flights or the precise role played by travel in the onset of VTE.²³ To clarify this role, it would be necessary to obtain

additional data on other possible causative factors, including immobilization, venous compression, dehydration, and changes in aircraft cabin pressure. Studies undertaken to identify asymptomatic thrombotic events found an incidence of 1% to 2.2%.^{23,34}

The following clinical studies have been carried out: 6 with GCS, 2 with enoxaparin 40 mg/d, and 1 with acetylsalicylic acid 400 mg.^{2,25} The studies investigating the use of GCS suffered from methodological limitations, but the total number of thrombotic events in patients not using such measures was 3.7%, compared to 0.2% in patients using GCS.² No thrombotic events occurred in a group of 184 passengers who took enoxaparin 2 to 4 hours before travel, but taking aspirin 12 hours before travel and for 3 days after the flight did not afford any protection.^{2,25}

– Long-distance travelers (more than 6 hours) should receive the following recommendations: to avoid constrictive clothing around the extremities and waist; to avoid dehydration; and to stretch calf muscles frequently during flights (B).

– Travelers with additional risk factors should use GCS with pressure around the knee of 14-30 mm Hg or should receive a single high-dose injection of LMWH before the flight (Table 4) (C).

– The use of acetylsalicylic acid is not recommended for the prevention of VTE in long-distance travelers (B).

REFERENCES

- Grupo Multidisciplinar para el Estudio de la Enfermedad Tromboembólica en España. Estudio sobre la enfermedad tromboembólica venosa en España. Madrid: Imago Concept Image DEV; 2006.
- Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CS, et al. Prevention of venous thromboembolism: The seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004 Sep;126 (Suppl 3):S338-400.
- Alonso Ortiz del Río C, Medrano Ortega FJ, Romero Alonso A, Villar Conde E, Calderón Sandubete E, Marín León I, et al. Guía PRETEMED 2003. Guía de profilaxis de enfermedad tromboembólica en patología médica. Córdoba: SADEMI; 2003.
- National Institute for Health and Clinical Excellence (NICE). Guideline development methods – Appendix B. London: NICE; 2006 [cited 18/11/ 2006]. Available from: <http://www.nice.org.uk/>
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
- Horlocker TT, Wedel DJ, Benzon H. Regional anaesthesia in the anticoagulated patient: defining the risks (The Second ASRA Consensus Conference on Neuroaxial Anesthesia and Anticoagulation). *Reg Anesth Pain Med*. 2003;28:172-97.
- Lumpkin M. From the FDA. *Anesthesiology*. 1998;88:27A-28A.
- Llaur JV, De Andrés J, Gomar C, Gómez-Luque A, Hidalgo F, Torres LM. Guía clínica de fármacos inhibidores de la hemostasia y anestesia regional neuroaxial. *Rev Esp Anestesiología Reanim*. 2005; 52:413-20.
- Freedman KB, Brookenthal KR, Fitzgerald RH Jr, Williams S, Lonner JH. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J Bone Joint Surg Am*. 2000; 82:929-38.
- Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty: pneumatic plantar compression and aspirin compared with aspirin alone. *J Bone Joint Surg Am*. 1996;78:826-34.
- Bouthier J. The venous thrombotic risk in nonsurgical patients. *Drugs*. 1996;52:16S-29S.
- Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. *Chest*. 2000;118:1680-4.
- Monreal M, Kakkar AK, Caprini JA, Barba R, Uresandi F, Valle R, et al; RIETE Investigators. The outcome after treatment of venous thromboembolism is different in surgical and acutely ill medical patients. Findings from the RIETE registry. *J Thromb Haemost*. 2004;2:1892-8.
- Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med*. 1999;341:793-800.
- Cohen AT. Venous thromboembolic disease management of the nonsurgical moderate and high-risk patient. *Semin Hematol*. 2000;37: 19S-22S.
- Lutz L, Haas S, Hach-Wunderle V. Venous thromboembolism in internal medicine: risk assessment and pharmaceutical prophylaxis: publication for the specialist platform. *Med Welt*. 2002;53: 231-4.
- Gallus AS, Hirsh J, Tuttle RJ, Trebilcock R, O'Brien SE, Carroll JJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. *N Engl J Med*. 1973;288:545-51.
- Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ; PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110:874-9.
- Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmuller A, Juillard-Delsart D, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost*. 2000;83:14-9.
- Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, Turpie AG, Egberts JF, Lensing AW; ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332:325-9.
- Hull RD, Schellong SM, Tapson VF, Monreal M, Samama MM, Turpie AG, et al. Extended-duration thromboprophylaxis in acutely ill medical patients with recent reduced mobility: methodology for the EXCLAIM study. *J Thromb Thrombolysis*. 2006;22:31-8.
- Lapostolle F, Surget V, Borron SW, Desmaizieres M, Sordelet D, Lapandry C, et al. Severe pulmonary embolism associated with air travel. *N Engl J Med*. 2001;345:779-83.
- Hughes BJ, Hopkins RJ, Hill S. Frequency of venous thromboembolism in low to moderate risk long distance travellers: the New Zealand Air Traveller's Thrombosis (NZATT) study. *Lancet*. 2003;362:2039-44.
- Pérez-Rodríguez E, Jiménez D, Díaz G, Pérez-Walton I, Luque M, Guillén C, et al. Incidence of air travel-related pulmonary embolism at the Madrid-Barajas airport. *Arch Intern Med*. 2003;163: 2766-70.
- Cesarone MR, Belcaro G, Nicolaidis AN, Incandela L, De S, Geroulakos G, et al. Venous thrombosis from air travel: the LONFLIT3 study – prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. *Angiology*. 2002;53:1-6.

Abbreviations

COPD	Chronic obstructive pulmonary disease
DVT	Deep vein thrombosis
GCS	Graduated compression stockings
INR	International normalized ratio
IPC	Intermittent pneumatic compression
LDUFH	Low dose unfractionated heparin
LMWH	Low-molecular-weight heparin
SEPAR	Spanish Society of Pulmonology and Thoracic Surgery
VTE	Venous thromboembolic disease

APPENDIX 1

Methods

Overall Approach

A multidisciplinary working group was formed comprising 3 respiratory specialists (1 of whom coordinated the project), 2 internists, 1 hematologist, 1 chest surgeon, and 1 expert in health sciences research methodology.

1. The present guidelines are based on 2 published documents: the most recent recommendations of the American College of Chest Physicians (ACCP) based on the Seventh Consensus Conference on Antithrombotic and Thrombolytic Therapy and the PRETEMED 2003 guidelines on prophylaxis in medical patients.^{2,3} Consequently we have used the classification systems for stratifying risk in different surgical and medical circumstances specified in these 2 documents.

2. To update these recommendations, we undertook a systematic review of the literature published between October 2003 and September 2006 focusing on 2 main research topics: the risk of venous thromboembolism associated with each disease or clinical circumstance; and the effectiveness of prophylactic intervention in reducing such risk without giving rise to serious adverse effects. Each of the articles selected in the course of this search was then analyzed by 2 members of the working group, who jointly assessed the quality of the evidence presented.

We had to standardize the system used to grade the strength of recommendations taken from the 2 clinical guideline documents used as the initial basis of the present guidelines and those drawn up on the basis of the evidence found in the literature review carried out by the working group. We used the criteria followed by the authors of the PRETEMED 2003 guide and adapted the ACCP recommendations for surgical patients and the new evidence found to this classification.

3. Finally, given the concurrence of risk factors, particularly in medical patients, we decided to add the tool provided by the PRETEMED 2003 guide for assessing patients on a case-by-case basis.

A draft document was drawn up, which was then approved by consensus among the members of a multidisciplinary panel of external reviewers (see Appendix 2). The opinion of patients was not sought in drawing up the recommendations contained in these guidelines.

Literature Search Strategy

The literature search was carried out by using key words for each disease to search MEDLINE, EMBASE, and the Cochrane Library for articles published between October 2003 and September 2006. A further manual search was also undertaken on the basis of the articles and clinical practice guidelines found in the initial search. The studies identified were then analyzed and selected if they were considered to provide answers to the initial research questions posed (risk of venous thromboembolism, effectiveness of the intervention, and the complications associated with the prophylactic measures taken).

Methodologic Quality

The quality of each study was analyzed using the comparative list provided by the National Institute for Health and Clinical Excellence (NICE) for the evaluation and critical reading of scientific studies and a quantitative method based on the Jadad scale for the assessment of reports on risk and interventions.^{4,5} On the basis of these 2 scales, we were able to assign a score to the quality of the evidence provided by each article using a 7-point scale and the following stratification: 0-2, low strength evidence; 3-4, intermediate; 5-6, high; and 7, excellent. Two researchers who were not members of the working group critically assessed the articles proposed for inclusion, and disagreements were settled by consensus. Using these assessment tools, it was possible to determine the validity of a study (the criteria used to define the sample population, prospective data collection, and how the stated outcomes were measured) and to its applicability to each patient.

Grading of Recommendations

The recommendations for each disease were graded according to the strength of the evidence on which they were based and the effect of the intervention in terms of the risk-benefit balance.³ Each recommendation can therefore be assigned to one of the cells in the following table:

Quality of Evidence	Expected Effect of the Intervention (Risk/Benefit)			
	Substantial	Marked	Small	None
High	A	A	B	D
Intermediate	B	B	C	D
Low	C	C	D	D
Unknown	No evidence	No evidence	No evidence	No evidence

Modified from Alonso Ortiz del Río et al.³

The grading of recommendations taken from the ACCP guidelines for surgical patients was adapted to the scheme shown in the Table based on the quality of evidence and information given by the ACCP.² This was done to standardize the classification of proposed recommendations. Appendix 3 shows the correspondence between the 2 grading systems.

Development of a Weighted Risk scale for Medical Patients

The PRETEMED guide developed a risk scale to quantify overall risk in each medical patient and to evaluate the need for prophylaxis. This scale was based on data on the incidence or absolute risk of venous thromboembolic disease associated with each factor. The scale was adjusted after the indications for prophylaxis were validated by consensus among a panel of experts.³ This risk scale for venous thromboembolic disease in medical patients and the type of prophylaxis recommended for each risk level is shown in Appendix 4.

APPENDIX 2
Panel of External Reviewers

Dr Juan Ignacio Arcelus Martínez (General Surgery, Hospital Universitario Virgen de las Nieves, Granada)
 Dr Manuel Arenas Gordillo (Respiratory Medicine, Hospital de Jerez, Jerez de la Frontera)
 Dr Raquel Barba Martín (Internal Medicine, Fundación Hospital de Alcorcón, Madrid)
 Dr Ana Blanco Orozco (Chest Surgery, Hospital Universitario Virgen del Rocío, Sevilla)
 Dr José Blanquer Oliva (Intensive Care, Hospital Clínico, Valencia)
 Dr Miguel Ángel Cabezudo Hernández (Respiratory Medicine, Hospital Central de Asturias, Oviedo)
 Dr Francisco Conget López (Respiratory Medicine, Hospital Clínico Universitario Lozano Blesa, Zaragoza)
 Dr Teresa Elías Hernández (Respiratory Medicine, Hospital Universitario Virgen del Rocío, Sevilla)
 Dr Gemma Iruín Irulegui (Hematology and Hemotherapy, Hospital de Cruces, Barakaldo, Vizcaya)
 Dr José Luis Lobo Beristain (Respiratory Medicine, Hospital de Txagorritxu, Vitoria, Álava)
 Dr Juan Vicente Llau Pitarch (Anesthesiology, Hospital Clínico, Valencia)
 Dr Manuel Monreal Bosch (Internal Medicine, Hospital Germans Trias i Pujol, Badalona)
 Dr Mikel Oribe Ibáñez (Respiratory Medicine, Hospital de Galdakao, Vizcaya)
 Dr Consolación Rodríguez Matute (Respiratory Medicine, Hospital San Juan de Dios, Bormujos, Sevilla)
 Dr José Antonio Rodríguez Portal (Respiratory Medicine, Hospital Universitario Virgen del Rocío, Sevilla)
 Dr Javier Trujillo Santos (Internal Medicine, Hospital General Santa María del Rosell, Cartagena)
 Dr Silvia Vidal Serrano (Health Technology Assessment Agency of Andalusia)

REFERENCES

- Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M; Pegasus Investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg.* 2005; 92:1212-20.
- Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev.* 2000;3:CD001484
- Andtbacka RH, Babiera G, Singletary SE, Hunt KK, Meric-Bernstam F, Feig BW, et al. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. *Ann Surg.* 2006;243:96-101.
- Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005;293:715-22.
- Blom JW, Osanto S, Rosendaal FR. The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma. *J Thromb Haemost.* 2004;2:1760-5.
- Cook G, Depares J, Singh M, McElduff P. Readmission after hysterectomy and prophylactic low molecular weight heparin: retrospective case-control study. *BMJ.* 2006;332:819-20.
- Fuchs S, Heyse T, Rudofsky G, Gosheger G, Chylarecki C. Continuous passive motion in the prevention of deep-vein thrombosis. *J Bone Joint Surg.* 2005;87:1117-22.
- Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. *Chest.* 2002;122:1933-7.
- Handoll HH, Farrar MJ, McBurnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev.* 2002;4:CD000305.
- Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore).* 1999;78:285-91.
- Mauermann WJ, Shilling AM, Zuo Z. A comparison of neuroaxial block versus general anesthesia for elective total hip replacement: a meta-analysis. *Anesth Analg.* 2006;103:1018-25.
- Mismetti P, Laporte S, Darmon JY. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg.* 2001;88:913-30.
- Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, et al. An association between atherosclerosis and venous thrombosis. *N Engl J Med.* 2003;348:1435-41.
- Singelyn F. Extended thromboprophylaxis with fondaparinux after major orthopedic surgery of the lower limbs: the Expert study. *Blood.* 2005;106:abstract 282.
- Steele N, Dodenhoff RM, Ward AJ, Morse MH. Thromboprophylaxis in pelvic and acetabular trauma surgery. *J Bone Joint Surg.* 2005;87:209-12.
- Tincani E, Piccoli M, Turrini F, Crowther MA, Melotti G, Bondi M. Video laparoscopic surgery: is out-of-hospital thromboprophylaxis necessary? *J Thromb Haemost.* 2005;3:216-20.

APPENDIX 3
Correspondence Between the 2 Scales Used to Grade the Strength of Recommendations

ACCP Scale	Clarity of Risk-Benefit	Methodological Quality of Studies	Implications	Corresponding Classification in These Guidelines
1A	Clear	RCTs without important limitations	Strong recommendation that can be applied to most patients in most circumstances without reservation	A
1C+	Clear	No RCTs, but the results of RCTs carried out in other populations can be unequivocally extrapolated or the evidence from observational studies is overwhelming	Strong recommendation that can be applied to most patients in most circumstances	A
1B	Clear	RCTs with important limitations (inconsistent results or methodological flaws)	Strong recommendation, likely to apply to most patients	B
1C	Clear	Observational studies	Intermediate-strength recommendation	B
2A	Unclear	RCTs without important limitations	Intermediate-strength recommendation	B
2C+	Unclear	No RCTs, but the results of other RCTs can be extrapolated	Weak recommendation	C
2B	Unclear	RCTs with important limitations	Weak recommendation	C
2C	Unclear	Observational studies	Very weak recommendation, other alternatives may be equally reasonable	D

Abbreviations: ACCP, American College of Chest Physicians; RCT, randomized clinical trial.

APPENDIX 4

Risk of Venous Thromboembolism (VTE) Under Different Conditions and Recommendations for Prophylaxis ^a				
	1	2	3	4
Medical and relevant conditions	Pregnancy/puerperium. Severe paralysis of LLs Travel >6 h	Cancer Congestive heart failure Chronic renal failure, nephrotic syndrome Severe acute infection Thrombophilia ^b	Unstable COPD Acute CVA with paralysis of LL	Acute myocardial infarction
Drugs	Tamoxifen Raloxifene Hormone replacement therapy Oral contraceptives	Chemotherapy		
Local processes	Central venous catheter	History of DVT-VTE Splint or bandage on LLs		
Others	Age >60 years Obesity (BMI >28 kg/m ²) Current smoker >35 cigarettes/d Residence in an institution	Bedridden >4 d		
Risk Calculation ^c	Recommendations for VTE Prophylaxis			
	Recommendation			
1-3	Consider using physical preventive measures			
4	Physical measures or LMWH (moderate-risk dose) if the score is reached by combining medical conditions and other circumstances LMWH (high risk dose) if the score relates only to medical conditions			
>4	Prophylaxis with LMWH (high-risk dose)			

^aModified from Alonso Ortiz del Río et al.³

^bConsider type of thrombophilia on a case-by-case basis.

^cRisk is calculated by adding the total weighting score corresponding to medical and relevant conditions (first row) to the total score corresponding to any other risks present (second, third, and fourth rows regarding drugs, local process, and other circumstances).

Abbreviations: BMI, body mass index; CVA, cerebral vascular accident; DVT, deep vein thrombosis; LL, lower limbs; LMWH, low-molecular-weight heparin.