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.


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 preventative 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

The authors of these guidelines were members of a working group appointed by the group coordinator, an appointee of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Dr Medrano, Dr Calderón, Dr Uresandi, and Dr Otero participated, either as authors or as members of the external review panel, in the elaboration of the PRETEMED 2003 guide sponsored by Aventis, SA. This sponsorship did not generate any conflicts of interest or commercial relationship or dependence for any of these authors. The present guidelines were drawn up with the technical support of SEPAR and were not sponsored in any relationship or dependence for any of these authors. The present guidelines were drawn up with the technical support of SEPAR and were not sponsored in any relationship or dependence for any of these authors. The present guidelines were drawn up with the technical support of SEPAR and were not sponsored in any relationship or dependence for any of these authors. The present guidelines were drawn up with the technical support of SEPAR and were not sponsored in any relationship or dependence for any of these authors.

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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. 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. 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. 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 neuraxial anesthesia in patients receiving pharmacological prophylaxis (HBPM or fondaparinux). 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

<table>
<thead>
<tr>
<th>Risk Factors for Venous Thromboembolism</th>
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<tbody>
<tr>
<td>Recent major surgery</td>
</tr>
<tr>
<td>Recent fracture or immobilization with a plaster cast of the lower limbs</td>
</tr>
<tr>
<td>Recent immobilization as a result of illness: New York Heart Association functional class III-IV heart failure, COPD exacerbations, sepsis, acute cerebral vascular accident</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Prior history of venous thromboembolic disease, especially idiopathic</td>
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<tr>
<td>Cancer, especially with metastasis</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Pregnancy, puerperium</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Superficial venous thrombosis, varicose veins</td>
</tr>
<tr>
<td>Oral contraceptives, hormone replacement therapy, tamoxifen</td>
</tr>
<tr>
<td>Miscellaneous: polycythemia vera, thrombocytosis, paroxysmal nocturnal hemoglobinuria, nephrotic syndrome, inflammatory bowel disease, Behçet’s syndrome, lupus erythematosus, antipsychotic medication</td>
</tr>
</tbody>
</table>

### TABLE 2

<table>
<thead>
<tr>
<th>Available Methods for the Prophylaxis of Venous Thromboembolism</th>
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<tbody>
<tr>
<td>Pharmacological Treatments</td>
</tr>
<tr>
<td>Low-molecular-weight heparins: bemiparin, dalteparin, enoxaparin, nadroparin, tinzaparin</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>Antivitamins K: acenocoumarol, warfarin</td>
</tr>
<tr>
<td>Indirect factor Xa inhibitors (fondaparinux)</td>
</tr>
<tr>
<td>Physical or nonpharmacological methods</td>
</tr>
<tr>
<td>Intermittent pneumatic compression</td>
</tr>
<tr>
<td>Graduated compression stockings</td>
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<tr>
<td>Venous foot pump</td>
</tr>
</tbody>
</table>

... 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

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


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).
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 presenting with pulmonary embolism on scintigraphic scans carried out during the 2 weeks following surgery. Prophylaxis is, therefore, used routinely in this type of surgery.

2.7.2 Recommendations

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

- In patients undergoing hip 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:
  - 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 administered.
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 events and 70% to 80% of cases of fatal pulmonary embolism 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.

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.

Several randomized controlled trials have demonstrated the greater efficacy of prophylaxis with LMWH or LDUFH compared to placebo. Prophylactic doses of LMWH in medical patients are similar to those used in surgical patients with moderate-to-high risk. Several randomized controlled trials have demonstrated the greater efficacy of prophylaxis with LMWH or LDUFH compared to placebo.

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.
Acute neurological disease, or inflammatory bowel disease (Table 4) (A). LDUHF 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. 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. 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%.2,3,4

The following clinical studies have been carried out: 6 with GCS, 2 with enoxaparin 40 mg/d, and 1 with acetylsalicylic acid 400 mg.2,5 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).

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Abbreviations

COPD Chronic obstructive pulmonary disease
DVT Deep vein thrombosis
GCS Graduated compression stockings
INR International normalized ratio
IPC Intermittent pneumatic compression
LDUHF Low dose unfractionated heparin
LMWH Low-molecular-weight heparin
SEPAR Spanish Society of Pulmonology and Thoracic Surgery
VTE Venous thromboembolic disease
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. 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. 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. Each recommendation can therefore be assigned to one of the cells in the following table:

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Expected Effect of the Intervention (Risk/Benefit)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Substantial</td>
</tr>
<tr>
<td>High</td>
<td>A</td>
</tr>
<tr>
<td>Intermediate</td>
<td>B</td>
</tr>
<tr>
<td>Low</td>
<td>C</td>
</tr>
<tr>
<td>Unknown</td>
<td>No evidence</td>
</tr>
</tbody>
</table>

Modified from Alonso Ortiz del Río et al.

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. 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. 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 Rocio, 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 Rocio, Sevilla)
Dr Gemma Iruin 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 Mikael 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 Rocio, 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


APPENDIX 4

Risk of Venous Thromboembolism (VTE) Under Different Conditions and Recommendations for Prophylaxis

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical and relevant conditions</td>
<td>Pregnancy/puerperium.</td>
<td>Cancer</td>
<td>Unstable COPD</td>
</tr>
<tr>
<td></td>
<td>Severe paralysis of LLs</td>
<td>Congestive heart failure</td>
<td>Chronic renal failure, nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Travel &gt;6 h</td>
<td>Severe acute infection</td>
<td>Thrombophilia</td>
</tr>
<tr>
<td>Drugs</td>
<td>Tamoxifen</td>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Raloxifene</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hormone replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral contraceptives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local processes</td>
<td>Central venous catheter</td>
<td>History of DVT-VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Splint or bandage on LLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Age &gt;60 years</td>
<td>Bedridden &gt;4 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity (BMI &gt;28 kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current smoker &gt;35 cigarettes/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Residence in an institution</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Calculation:

- 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)

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

APPENDIX 3

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

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

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