To assess the state of the art of venous thrombosis and pulmonary embolism for the medical and other health-related professions, the World Health Organization (WHO) and the International Society and Federation of Cardiology (ISFC) convened a task force in Geneva, Switzerland. Members of the task force prepared position papers and presented brief oral presentations. A report was subsequently prepared by the task force members, who contributed sections in their areas of expertise. Revisions of the report occurred both during the task force meeting itself in Geneva and during the ensuing months. The final report was approved by the WHO-ISFC Task Force on Pulmonary Embolism Steering Committee. More quantitative information is needed on the frequency of venous thrombosis and pulmonary embolism in hospitalized medical patients as well as in outpatients at high risk. Population studies should focus on incidence, survival, and long-term complications in different parts of the world with respect to gender and race. Further educational efforts are needed to increase awareness about venous thrombosis and pulmonary embolism prophylaxis. Finally, research into effective techniques for changing physician practice would be useful.

VENOUS THROMBOSIS (VT) and pulmonary embolism (PE) constitute some of the most common cardiopulmonary illnesses in North America and in Europe. In the United States, the death rate from PE is higher in men than in women and in nonwhites than in whites.

Women age 50 years and under in one study had a decreased frequency of PE compared with men. However, in the United States, PE is the most common medical cause of maternal mortality associated with live births.2 In North America and in Europe, death from PE occurs more frequently with increasing age. Contemporary autopsy studies reveal that PE continues to be underdiagnosed among hospitalized patients. Autopsy studies have shown that PE is especially difficult to diagnose ante mortem, particularly among elderly patients and among subjects with underlying cardiopulmonary disease.

Epidemiology

Unfortunately, estimated rates for VT and PE in population-based studies have been reported in only a few countries. Even available data must be analyzed carefully, because different diagnostic codes and criteria can be applied. The task force believes that there is an urgent need to develop clear criteria for assessment of VT and PE as well as for simple protocols that could be incorporated into studies currently being planned by the World Health Organization (WHO). Thus, further information should be collected regarding the frequency of VT and PE among different races and in different parts of the world. Risk factors for VT and PE can be either acquired (Table I) or due to primary hypercoagulable states, which can occasionally be
identified (Table 2). Pathologic studies have demonstrated that patients with thrombotic PEs have embolization most often to the lower lobes, whereas patients with primary thrombosis of lung blood vessels have pathologic findings more often in the upper lobes of the lung.

Table 1. Acquired conditions associated with pulmonary embolism.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
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<tbody>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Orthopedic</td>
</tr>
<tr>
<td>Gynecological cancer</td>
</tr>
<tr>
<td>Major abdominal</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>Renal transplantation</td>
</tr>
<tr>
<td>Splenectomy</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Immobilized patients</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td>Pregnancy/oral contraceptives</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Advanced age</td>
</tr>
<tr>
<td>Lupus anticoagulant/antithrombin antibodies</td>
</tr>
</tbody>
</table>

Table 2. Primary hypercoagulable states.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin III deficiency</td>
</tr>
<tr>
<td>Protein C deficiency</td>
</tr>
<tr>
<td>Protein S deficiency</td>
</tr>
<tr>
<td>Excessive plasminogen activator inhibitor</td>
</tr>
</tbody>
</table>

Autopsy Studies

An autopsy study from Malmo, Sweden, has demonstrated convincingly that the danger of postoperative PE continues for more than 1 month after surgery.4 Studies from London, England,5 and from Geneva, Switzerland,6 also indicate that the risk of VT of the legs and of PE continues for about 1 month after discharge. The authors of the Geneva study calculated that the rate of postoperative PE increases by 30% when PEs that occur within 30 days of hospital discharge are included.

In a Swedish autopsy study,7 the overall incidence of VT and PE did not change over a 30-year period. In 1987, the proportion of autopsy-proved fatal PE was found to have decreased significantly among orthopedic surgical patients. However, for other patients, the figures appear to be remarkably stable during the 30-year period that was analyzed. During this time, the proportion of the population aged over 65 years had doubled, and this may have masked the beneficial effects of prophylaxis. Future studies are needed that correct prevalence for age.

Future Directions

Populations studies of incidence, survival, and long-term complications from VT and PE in different parts of the world are needed to define the extent of the problem in the developing world. Gender- and race-specific data comparing areas of different disease incidence might also help to identify pathogenetic factors. Isolated calf vein thrombosis and upper-extremity thrombosis may be increasing in importance as antecedents to the development of PE, and their significance should be reevaluated. Basic research into the pathogenesis of thrombosis may make it possible to identify treatable hypercoagulable states among those who have VT and PE, with or without an obvious cause for their illness.

Diagnosis

Clinical Assessment

Clinical suspicion of PE is a prerequisite for its diagnosis. Clinical examination should include an assessment for findings of VT, such as localized or unilateral swelling of an extremity with or without pain, and for symptoms of PE, such as sudden onset of dyspnea or pleuritic chest pain. Diagnosis of PE should especially be considered in the presence of predisposing conditions (Table 1). When PE is suspected, chest roentgenograms and electrocardiograms may demonstrate signs that help differentiate PE from other conditions and reinforce clinical suspicion. Arterial blood gas evaluation, although not recommended as a diagnostic screening tool, may be of adjunctive value when a decrease in the PaO2 is observed. In the Prospective Investigation of Pulmonary Embolism Diagnosis, among patients without preexisting cardiopulmonary disease, there was no difference in room air P02 or in the alveolar-arterial oxygen gradient between those with PE at angiography and those with normal pulmonary angiograms who were suspected of having PE.

When patients present with chronic cor pulmonale, chronic PE should be considered as a
Thrombolysis

No laboratory test is available to predict in advance which patients who receive thrombolysis will suffer bleeding complications. Therefore, a careful history and physical examination to screen for potential complications is of paramount importance. Bleeding complications can be reduced by appropriate selection of patients and by minimizing the "handling" of patients during the thrombolytic infusion. For patients with high clinical suspicion for PE and high-probability ventilation-perfusion lung scans or echocardiographic evidence of thrombi in the main pulmonary arteries or in the right heart cavity, a clinician may elect to proceed with thrombolytic therapy even when the diagnosis has not been confirmed by angiography. Thrombolytic therapy should be administered through a peripheral vein rather than through a pulmonary artery catheter because the latter approach is neither safer nor more effective. When thrombolysis is administered to appropriate patients in the proper setting, the clinical response may be rapid and dramatically advantageous to the patient.

Hypotensive Patients

For patients with hemodynamic instability due to PE, (1) heparin therapy and/or thrombolysis; (2) pressor agents, such as norepinephrine; and (3) hemodynamic monitoring should be considered. If the systemic arterial pressure is not stabilized promptly in spite of the use of thrombolytic agents, pulmonary embolectomy might be utilized in selected patients, including those with severe chronic cor pulmonale, elevated pulmonary vascular resistance, and reduced cardiac output.

Oral Anticoagulation

Long-term anticoagulation is prescribed to avert recurrent VT and PE. Ordinarily, long-term anticoagulation is achieved with oral anticoagulation. In special circumstances - such as pregnancy, prior oral anticoagulation failure, or with cancer patients undergoing chemotherapy or suspected of having Trousseau's syndrome (thrombosis that is often migratory or recurrent) long-term high-dose subcutaneous heparin therapy may be utilized. When oral anticoagulation is initiated, the level of protein C may decline, creating a thrombogenic potential. By overlapping heparin therapy and oral anticoagulation for 4 or 5 days, this theoretical procoagulant effect of oral anticoagulation can be counteracted.

The prothrombin time is utilized to adjust the dose of oral anticoagulation. However, it is important that the prothrombin time results be reported according to the international normalized ratio (INR) rather than the prothrombin time ratio or the prothrombin time expressed in seconds. The reason is that, even within the United States and Canada, prothrombin time assays are carried out with a variety of thromboplastins that have markedly different sensitivities. The INR can be thought of, simplistically, as a "corrected prothrombin time." In actuality, the INR is the prothrombin time ratio that would be obtained if the WHO reference thromboplastin were always utilized to perform the prothrombin time test. Most available thromboplastins are supplied with a calibration factor known as the International Sensitivity Index (ISI). By utilizing the International Sensitivity Index, laboratories can express prothrombin time results in terms of the INR. For example, within North America, a prothrombin time of 18 seconds and prothrombin time ratio of 1.5 at one laboratory could be equivalent to a prothrombin time of 22 seconds and prothrombin time ratio of 1.8 at another laboratory. The same blood specimen in some European laboratories might yield a prothrombin time of 30 seconds and prothrombin time ratio of 2.5. Nevertheless, the INR for this same blood sample would be 3.0 at all laboratories, despite the three markedly different prothrombin time ratios and prothrombin times given in this example.

The target INR for oral anticoagulation of patients with PE should be at least 2.0 to 3.0, but heparin therapy/oral anticoagulation overlap should be maintained for at least 4 days, even if the target INR is achieved more quickly. Oral anticoagulation is usually continued for at least 3 to 6 months but may be administered indefinitely, particularly if underlying risk factors, such as cancer or massive obesity, have not been controlled. For patients who cannot tolerate heparin therapy or oral anticoagulation, an inferior vena caval filter should be inserted (see below).

In a few patients, PEs do not lyse but rather progress to chronic thromboembolic pulmonary hypertension, which is amenable to surgical
PULMONARY EMBOLISM

correction (endarterectomy of chronic, endothelialized thrombi). Under optimal circumstances, this operation has a mortality rate of 13%.26 Long-term results from this surgery are outstanding.27

Future Directions

Several questions remain about the most appropriate therapy for PE and VT: (1) the role of low-molecular-weight heparins and newer antithrombin agents, such as hirudin, in established VT and PE, and (2) the role of pulmonary embolectomy in life-threatening as well as in subacute PE. In particular, catheter embolectomy appears to be a promising technique.28

Prevention

It is easier and less expensive to prevent PE than to diagnose and to treat it. Virtually all hospitalized adult patients, particularly after major surgery, and all women after delivery should receive prophylactic measures against venous thromboembolism. The method of PE prevention that is utilized should be based on an assessment of the patient's level of risk for PE and on whether a patient is most likely to benefit from nonpharmacologic (Table 3), pharmacologic (Table 4), or combined (Table 5) modalities. Because the risk of PE continues after discharge from the hospital, prophylaxis should be continued at home among those patients at moderate or high risk for venous thromboembolism.

Table 3. Nonpharmacologic approaches to pulmonary embolism prophylaxis.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graduated compression stockings (GCS)</td>
<td>Prevent venous stasis</td>
</tr>
<tr>
<td>Intermittent pneumatic compression (IPC)</td>
<td>Prevent venous stasis</td>
</tr>
<tr>
<td>Inferior vena caval interruption</td>
<td>Preven venous stasis, increase endogenous fibrinolytic activity Prevents pulmonary embolism by mechanical blocking effect but does not prevent deep venous thrombosis</td>
</tr>
<tr>
<td>Combined nonpharmacologic methods (eg, GCS plus IPC)</td>
<td>Additive or synergistic effect</td>
</tr>
<tr>
<td>Combined nonpharmacologic plus pharmacologic approach (eg, IPC boots plus low-dose heparin)</td>
<td>Additive or synergistic effect</td>
</tr>
</tbody>
</table>

Table 4. Pharmacologic prophylaxis.

<table>
<thead>
<tr>
<th>Unfractionated low-dose subcutaneous heparin</th>
<th>Recommended Pulmonary Embolism Prophylaxis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-molecular-weight heparin</td>
<td></td>
</tr>
<tr>
<td>Dextran</td>
<td></td>
</tr>
<tr>
<td>Adjusted-dose warfarin (orthopedic surgery)</td>
<td></td>
</tr>
<tr>
<td>Very-low-dose warfarin</td>
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</tbody>
</table>

Table 5. Recommendations for pulmonary embolism prophylaxis among special high-risk groups.

<table>
<thead>
<tr>
<th>High-Risk Group</th>
<th>Recommended Pulmonary Embolism Prophylaxis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopedic surgery in lower extremity</td>
<td>IPC boots plus pharmacologic prophylaxis, followed by some type of prophylaxis after hospital discharge</td>
</tr>
<tr>
<td>Gynecologic cancer surgery</td>
<td>IPC boots and/or intensive pharmacologic prophylaxis</td>
</tr>
<tr>
<td>General surgery</td>
<td>Combined nonpharmacologic or combined nonpharmacologic plus pharmacologic modalities</td>
</tr>
</tbody>
</table>

*IPC indicates intermittent pneumatic compression.

The most commonly used nonpharmacologic measures are graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) boots. Overall, there are five nonpharmacologic approaches to PE prophylaxis, including several strategies that combine various preventive modalities (Table 3).

Graduated Compression Stockings

GCS often have 18 mm Hg of compression at the ankle, 14 mm Hg at the calf, 8 mm Hg at the knee, 10 mm Hg at the lower thigh, and 8 mm Hg at mid thigh. Among low-risk general surgery patients, GCS can reduce the frequency of VT by more than half compared with no prophylaxis.29 GCS should be considered as first-line prophylaxis against PE among all hospitalized patients except for those with peripheral arterial disease, whose condition may be worsened by vascular compression. Care should be taken to avoid a tourniquet effect at the proximal portion of the stockings.

IPC Boots

IPC boots provide intermittent inflation of air-filled cuffs that prevent venous stasis in the legs
and appear to stimulate the endogenous fibrinolytic system. Intermittent gradient compression (eg, pressures of 35, 30, and 20 mm Hg at the ankle, calf, and thigh, respectively, applied sequentially) more than doubles the peak blood-flow velocity in the legs.

Inferior Vena Caval (IVC) Interruption

IVC interruption is usually accomplished with a filter device that mechanically blocks clinically important thrombus that arises in lower-extremity and pelvic veins and thus prevents PE while maintaining patency of the IVC. These devices have no effect on the thrombotic process and do not prevent VT of the upper extremities, pelvis, or deep leg veins.

The three main indications for interruption of the IVC (1) contraindication to anticoagulant therapy, (2) failure of anticoagulation, and (3) in unusual circumstances, prophylaxis among extremely high-risk patients (eg, hip fracture surgery after recent PE or chronic severe pulmonary hypertension due to prior PE). Selection of the appropriate filter is crucial. The factors for consideration include the ability to retain major blood clots, high IVC patency, and minimal complications. Among the better known filters are the Kimray-Greenfield, titanium Greenfield, bird's nest, LGM Nena Tech, Simon-Nitinol, and Gunther filters. The particular needs of individual patients should be taken into account. For example, when there is full life expectancy, a filter tested over a long period, such as the Greenfield filter, can be used. When the IVC is larger than 30 mm in diameter, the bird's nest filter is often employed. The Simon-Nitinol filter, with its small carrier, is particularly suitable when the femoral veins are small.

We believe that a well-coordinated team (preferably consisting of a vascular surgeon, interventional radiologist, cardiologist, and/or vascular medicine specialist), all comprehensively and specifically trained, is the most effective way to secure the best possible results for the patient and learning experience for trainees. New randomized prospective studies are warranted to define exactly the role of the existing devices and contribute toward the development of new ones, even more effective and with fewer complications. Further development of retrievable filters would be useful in selected patients.

Combined Nonpharmacologic Methods

The two nonpharmacologic methods of GCS and IPC may work through complementary mechanisms. GCS provide continuous stimulation of linear blood-flow velocity and prevent dilation of the venous system in the legs. IPC devices compress the veins more forcefully than GCS but for a relatively brief period. In a randomized trial of patients undergoing general surgery, GCS plus IPC boots were more effective than IPC boots alone in preventing VT.

Combined Nonpharmacologic Plus Pharmacologic Approach

Vascular compression to prevent venous stasis and low-dose heparin administration to prevent hypercoagulability are prophylaxis strategies that can be combined in moderate- or high-risk patients. Among patients undergoing general surgery, several studies have demonstrated that GCS plus low-dose heparin is more effective than low-dose heparin alone in reducing the frequency of VT. In a meta-analysis of 45 randomized controlled trials of deep VT prophylaxis among general surgery patients without cancer, combined modalities were found to be more effective than any single prophylaxis method. Based on a very small number of studies, IPC plus GCS resulted in the lowest rate of postoperative deep VT, only 4.5% (95% confidence interval, 1.1% to 8.0%). GCS plus low-dose heparin administration had a deep VT rate of 6.3% (95% confidence interval, 0% to 17.6%).

Pharmacologic Prophylaxis

Unfractionated Low-Dose Subcutaneous Heparin

The most comprehensive randomized controlled trial of low-dose heparin prophylaxis (5000 U of subcutaneous heparin 2 hours preoperatively and every 8 hours thereafter for 7 days) as prophylaxis against fatal postoperative PE was organized by Kakkar in the International Multicentre Trial involving 4121 patients. Eligible patients were over age 40 years and were scheduled to undergo elective major surgery. Of the autopsied subjects, 16 controls died of PE vs only two patients in the heparin group. Although more wound hematomas occurred among heparin-treated patients, the number of deaths due to hemorrhage was not increased among those who received heparin.
Collins and colleagues38 reviewed data from 78 randomized controlled trials with 15 598 patients, confirming the International Trial Multicentre result. There was a 40% reduction in nonfatal PE and a 64% reduction in fatal PE among heparin-treated patients. The heparin-treated patients also had about one third as many instances of VT as control patients, regardless of whether they had undergone general, urological, elective orthopedic, or traumatic orthopedic surgery. There was no significant difference in fatal hemorrhage between the heparin and control groups. Although excessive bleeding was more likely to occur among patients assigned to heparin prophylaxis - especially those who underwent urological procedures - the absolute excess in bleeding was only about 2%.

**Low-Molecular-Weight Heparins**

Low-molecular-weight heparin therapy has three major potential advantages over unfractionated heparin therapy: (1) a lower frequency of bleeding, (2) effective prophylaxis with administration only once daily, and (3) greater efficacy.39 The low-molecular-weight heparins have a higher bioavailability and extended plasma half-life compared with unfractionated heparin and may be effective as once-daily subcutaneous injections instead of injections two or three times daily, which are required for prophylaxis with unfractionated heparin. In a double-blind British study comparing low-molecular-weight heparin with unfractionated heparin prophylaxis among 295 patients undergoing elective major abdominal surgery, the rate of deep VT as detected on leg scanning with fibrinogen labeled with iodine 125 was 2.5% among those who received low-molecular-weight heparin compared with 7.5% among those who received unfractionated heparin (P < .05).40 A recent meta-analysis found a 20% lower rate of VT with low-molecular-weight heparin prophylaxis.41 Low-molecular-weight heparin is also very effective in preventing deep VT among patients undergoing elective hip surgery vs placebo42; vs unfractionated heparin, 7500 U twice daily43; or vs adjusted-dose unfractionated heparin three times daily.44 Current evidence does not indicate an increased risk of bleeding when low-molecular-weight heparins are employed in combination with epidural or spinal anesthesia. However, each of the various low-molecular-weight heparins has a distinct pharmacologic profile and should be standardized against the WHO-endorsed low-molecular-weight heparin standard.

**Dextran**

This glucose polymer impairs platelet function by causing decreased platelet aggregability. Potential adverse effects include anaphylaxis, volume overload, nephrotoxicity, and, paradoxically, bleeding. Its particular niche appears to be among patients who require pharmacological prophylaxis but who are unable to receive heparin prophylaxis because of bleeding or other adverse reactions to heparin, such as heparin-associated thrombocytopenia.

**Adjusted-Dose Warfarin**

In patients at high risk, adjusted-dose warfarin prophylaxis may be appropriate. In a randomized trial at McMaster University, Hamilton, Ontario, adjusted-dose warfarin prophylaxis (target INR, 2.0 to 2.7) reduced the frequency of VT in patients who had undergone surgery for hip fractures to 20% compared with 46% in the placebo group.45

**Very-Low-Dose Warfarin**

Fixed very-low-dose warfarin (1 mg daily) can reduce the frequency of in-dwelling catheter thrombosis46 and of VT among patients undergoing major gynecologic surgery.47 Further trials, however, are needed before its use is recommended.

**Approach for Special High-Risk Groups**

Orthopedic Surgery - These patients are at very high risk. In a randomized controlled trial48 of sequential gradient IPC boots vs adjusted low-dose warfarin prophylaxis (target INR, approximately 2.0) among patients undergoing total hip replacement, the nonpharmacologic and pharmacologic modalities had similar efficacy. The end point was venographically confirmed deep VT of the legs, and the frequency of deep VT was 17% in each group. In a more recent study of patients with total hip replacement, the venographic ally confirmed deep VT rates were 27% for IPC boots and 31% for warfarin prophylaxis.49 Orthopedic patients should be considered for combined nonpharmacologic and pharmacologic prophylaxis while hospitalized, followed by some form of prophylaxis for approximately 1 month after hospital discharge. Alternatively, predischarge
ultrasonography could be performed on all patients, and those without deep VT might not require further prophylaxis. 50 Patients undergoing total knee replacement are at as high a risk of developing PE as patients undergoing total hip replacement. 51

Gynecologic Cancer Surgery - Patients who develop proximal-leg deep VT and PE after gynecologic cancer surgery often have no evidence of calf vein thrombosis. The thrombi appear to arise de novo in the pelvic or proximal deep veins of the leg. 52 Nonpharmacological prophylaxis, if utilized, should consist of IPC boots. If pharmacological prophylaxis is selected, intensive fixed low-dose heparin (5000 U subcutaneously three times daily) is suggested.

Immobilized Medical Patients - Among bedridden patients in a respiratory intensive care unit, one study found that PE occurred in 27% who underwent autopsy. 53 Half of these PEs were not diagnosed before death. In another study, among immobilized patients who were not critically ill, fibrinogen leg scanning identified deep VT in 13%. 54 Therefore, immobilized medical patients should routinely receive nonpharmacologic or pharmacologic prophylaxis.

Cost-effectiveness of PE Prevention
Prophylaxis not only saves lives but also is cost-effective. In an analysis of patients undergoing major orthopedic surgery, all prophylaxis methods saved health care dollars. 55 In a separate analysis of general surgery patients, the most cost-effective approach was GCS. 56

New Agents to Prevent VT
Specific antithrombin drugs that are being developed, such as hirudin, have promise in the prevention of venous thrombosis.

Summary of Prevention
Prophylaxis against VT and PE continues to be underutilized, despite the availability of effective nonpharmacologic and pharmacologic methods. 57 A recent meta-analysis suggests that antiplatelet agents may also be effective and that their utility should be examined (Antiplatelet Trialists' Collaboration, unpublished data). The task force endorses the intensification of prophylaxis efforts, with particular attention to special high-risk patients during hospitalization and for the first month after hospital discharge. The task force believes that all clinicians should review the thromboprophylaxis policy at their institutions and should devise a system in which the risk for every hospitalized patient is assessed preoperatively. Safeguards should be set up to ensure that appropriate prophylaxis is offered to all patients at special risk for VT or PE. Especially in high-risk patients, clinicians should consider extending the prophylactic period to cover the first month after hospital discharge.

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References


