Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis (JCS 2009)
– Digest Version –
JCS Joint Working Group

Table of Contents

Abbreviations Used in the Guidelines .......................... 1258
Introduction to the Revised Guidelines ....................... 1259
I General Descriptions ........................................ 1259
1. Acute Pulmonary Thromboembolism ..................... 1259
2. Chronic Pulmonary Thromboembolism ................. 1261
3. Deep Vein Thrombosis .................................... 1262
II Descriptions of Individual Diseases .................... 1263
1. Acute Pulmonary Thromboembolism ..................... 1263
2. Chronic Pulmonary Thromboembolism ................. 1268
3. Deep Vein Thrombosis .................................... 1272
4. Prevention of Pulmonary Thromboembolism/ Deep Vein Thrombosis (Venous Thromboembolism) .... 1275
References .................................................... 1277

Abbreviations Used in the Guidelines

AaDO: alveolar-arterial oxygen difference
ACE: angiotensin converting enzyme
APTT: activated partial thromboplastin time
BNP: brain natriuretic peptide
CABG: coronary artery bypass grafting
CT: computed tomography
CTEPH: chronic thromboembolic pulmonary hypertension
CTR: cardiothoracic ratio
DBP: diastolic blood pressure
DVT: deep vein thrombosis
HTC: hematocrit
HIT: heparin-induced thrombocytopenia
HLA: human leukocyte antigen
HOT: home oxygen therapy
ICU: intensive care unit
INR: international normalized ratio
IPC: intermittent pneumatic compression
IVC: inferior vena cava
MDCT: multi-detector CT
MHLW: Ministry of Health, Labour and Welfare
MRA: magnetic resonance angiography
MRV: magnetic resonance venography
MSCT: multi-slice CT
NHI: National Health Insurance
NO: nitric oxide
NYHA: New York Heart Association
PaCO2: partial pressure of arterial carbon dioxide
PaO2: partial pressure of arterial oxygen
PCPS: percutaneous cardiopulmonary support
PE: pulmonary embolism
PEA: pulmonary thromboendarterectomy
PEEP: positive end-expiratory pressure
PG: prostaglandin
PH: pulmonary hypertension
PT: prothrombin time
PTCA: percutaneous transluminal coronary angioplasty
PTE: pulmonary thromboembolism
SBP: systolic blood pressure
SpO2: peripheral oxygen saturation
UK: urokinase
VTE: venous thromboembolism

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This English language document is a revised digest version of Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis reported at the Japanese Circulation Society Joint Working Groups performed in 2008. (website: http://www.j-circ.or.jp/guideline/pdf/JCS2009_guideline.pdf)
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The Japanese Circulation Society (JCS) has already provided guidelines for the diagnosis and treatment of major cardiovascular diseases. The JCS decided to revise the Guidelines for the Diagnosis, Treatment and Prevention of Pulmonary Thromboembolism and Deep Vein Thrombosis, which were first completed in April 2004, to include new advanced techniques of diagnosis and treatment of these conditions that have been developed since publication of the first guidelines. As was the case for the previous guidelines, the Working Groups for the present guidelines consisted of cardiologists and cardiovascular surgeons who have been involved in research on the diagnosis, treatment and prevention of pulmonary thromboembolism (PTE).

Although the etiology and pathology of PTE have yet to be completely determined, it is known that deep vein thrombosis (DVT) plays an important role in the development of PTE. PTE may thus be considered a complication of DVT, and these conditions are regarded as a single disease entity that should be called venous thromboembolism (VTE). Treatment for PTE differs significantly depending on whether the condition is acute or chronic. Although acute PTE is an emergent condition especially prevalent in Europe and the United States, it is becoming increasingly prevalent in Japan as well because of Westernization of Japanese lifestyle, the rapid increase in population of the elderly, increased recognition of this disease, and advancement of diagnostic techniques. Acute PTE has received much media attention as an economy-class syndrome and an unexpected secondary disaster following earthquakes. It is also a postoperative complication that should be carefully monitored for in patients with prolonged bed rest following gastrointestinal surgery, gynecologic treatment, or orthopedic surgery. Patients with acute PTE require prompt diagnosis and appropriate treatment. Patients with acute PTE often respond well to thrombolytic therapy and anticoagulation therapy, and new drugs have been approved and are available for this patient population. Patients with large amounts of thrombus or circulatory collapse can be treated effectively with catheterization and surgery. Inferior vena cava (IVC) filters are used to prevent PTE, and the use of non-permanent filters (also referred to as temporal filters and removable filters) has become increasingly common. Chronic PTE associated with pulmonary hypertension (PH) is a serious condition that causes right heart failure and respiratory failure and does not respond well to conventional medical treatment. However, its prognosis has been improved by new drugs efficacious in the treatment of PH. Pulmonary thromboendarterectomy (PEA) with cardiopulmonary bypass and deep hypothermic intermittent circulatory arrest is performed as radical treatment of PTE, and has significantly improved the outcome of surgery, clinical symptoms, and cardiopulmonary hemodynamics as well as the QOL of patients with central type of chronic PTE. Prevention of perioperative VTE by physical therapy is quite important, and new drugs have become available for this purpose.

The Working Groups revised the present guidelines, placing emphasis on currently available evidence whenever possible, but it should be noted that the present guidelines include up-to-date information that may be utilized by cardiologists, cardiovascular surgeons, and other surgeons involved in surgical treatment of VTE in the clinical setting as guidance for diagnosis and treatment of this disease. It should also be noted that determination of treatment by attending physicians based on the specific conditions and circumstances of their patients should take precedence over the guidelines, and that the present guidelines provide no grounds for argument in cases of legal prosecution. The guidelines may be revised in the future to include description of newer methods of diagnosis and treatment of VTE.

We hope that the guidelines will aid physicians in the diagnosis, treatment, and prevention of VTE.

In the present guidelines, levels of recommendation are rated according to the following classification as used in other guidelines for the Diagnosis and Treatment of Cardiovascular Diseases.

Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of a procedure or treatment.

Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is general agreement that a procedure/treatment is neither useful nor indicated and may be harmful.

### 1. Acute Pulmonary Thromboembolism

**1 Epidemiology**

PTE becoming prevalent in Japan, and should no longer be considered a rare condition. In 2006, PTE occurred in 7,864 patients in Japan. The number of patients has increased 2.25-fold in the past decade,1 and the incidence of this condition is estimated to be 62 cases/million population. Since the incidence of PTE in the United States is about 500 cases/million population, that in Japan in 2006 is about one-eighth that in the United States.

The incidences of perioperative PTE in Japan were 4.41, 4.76, 3.62, and 2.79 cases/10,000 surgeries in 2002, 2003, 2004, and 2005, respectively. The incidence began to decrease in 2004 when the guidelines for the prevention of PTE were published and healthcare costs for preventive treatment began to be covered by the National Health Insurance (NHI) of Japan.2 In Japan, acute PTE develops more frequently in females than in males. The most common age of onset is in the sixth and seventh decades.3

**2 Risk Factors**

Major risk factors for PTE are listed in Table 1. Virchow’s triad, ie, the presence of (1) interrupted blood flow, (2) endo-

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**Classifications**

- **Class I:** Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
- **Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of a procedure or treatment.
- **Class IIa:** The weight of evidence/opinion is in favor of usefulness/efficacy.
- **Class IIb:** Usefulness/efficacy is less well established by evidence/opinion.
- **Class III:** Conditions for which there is general agreement that a procedure/treatment is neither useful nor indicated and may be harmful.
3 Conditions of Onset
Acute PTE often occurs when patients stand up or begin walking or during micturition or defecation after resting. Since the major source of emboli is thrombi in veins of the lower limbs or intrapelvic veins, it is believed that muscle contraction in the lower limbs increases venous return, with the muscles acting in a pump-like fashion to push blood, resulting in release of thrombi that cause PTE.

4 Pathophysiology
Acute PTE is caused by abrupt blockage of pulmonary vessels by thrombi that has formed in the veins or the heart and has traveled through the blood stream. The source of emboli is the veins of the lower limbs or pelvis in more than 90% of cases. The main manifestations of acute PTE are sudden onset of PH and hypoxemia. Since the mean pulmonary arterial pressure that can be generated by the right ventricle is 40 mmHg in individuals without cardiopulmonary disease, physicians should suspect acute-on-chronic PTE, ie, acute exacerbation of chronic PTE due to the occurrence of acute PTE, or chronic PTE. Pulmonary infarction, which occurs as a hemorrhagic infarction, develops in about 10 to 15% of patients with acute PTE, often as a result of occlusion of a peripheral pulmonary artery.

5 Severity Classification
Since the prognosis and rate of recurrence of acute PTE differ significantly by the presence or absence of echocardiographic findings of pressure overload in the right ventricle, the severity of acute PTE is commonly classified according to clinical signs/symptoms and echocardiographic findings, as outlined in Table 2.

6 Prognosis and Clinical Course
According to available data in Japan, the mortality rate of
acute PTE is 14% overall, 30% among patients with cardiogenic shock (20% among those receiving thrombolytic therapy and 50% among those not receiving it), and 6% among patients without cardiogenic shock. According to data in Europe and the United States, the mortality rate of acute PTE is as high as 30% when it is not diagnosed and treated promptly, but decreases to 2 to 8% when appropriate treatment is performed. It is known that early diagnosis and appropriate treatment decrease the mortality rate substantially. Independent determinants of mortality of acute PTE include right ventricular dysfunction on echocardiography, advanced age (≥70 years), cancer, congestive heart failure, chronic obstructive pulmonary disease, hypotension, and tachypnea.

In a follow-up study in Japan, PH developed in 3.7% in patients with acute PTE. In the United States, it has been estimated that PH secondary to chronic PTE develops in 0.1 to 3.8% of patients with a history of acute PTE.

### 2. Chronic Pulmonary Thromboembolism

#### 1 Definition

Chronic PTE develops as a result of chronic occlusion of pulmonary arteries by organized thrombi. In Japan, chronic PTE is defined as abnormal pulmonary blood flow distribution and pulmonary circulation hemodynamics that persist for ≥6 months without substantial changes. Some patients with chronic PTE exhibit clinical manifestations such as shortness of breath during exercise (exertional dyspnea) due to thrombotic occlusion of several pulmonary arteries, which causes PH. This condition is referred to as chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is classified by clinical course into two types, ie, recurrent CTEPH with a history of signs/symptoms suggestive of acute PTE, and latent CTEPH with progression of PH but without clear clinical findings of acute PTE. Patients with mild CTEPH are treated with medical treatment mainly consisting of anticoagulation therapy to prevent progression of disease, while patients with severe PH may also have right heart failure and a poor prognosis. In 1998, the Ministry of Health, Labour and Welfare (MHLW; formerly Ministry of Health and Welfare) of Japan termed CTEPH “idiopathic chronic PTE with PH” and designated it a specific disease for which healthcare costs are covered by public expenditure. In the present guidelines, however, the term CTEPH is used.

#### 2 Epidemiology

The incidence of PTE, including acute and chronic PTE, in Japan is believed to be lower than in Europe and the United States. According to data in annual reports on pathologic autopsy cases, the incidence of acute PTE in Japan is about one-tenth that in the United States, although these data are rather old. In the United States, it is estimated that acute PTE occurs in 0.5 to 0.6 million individuals each year, and that CTEPH occurs in about 0.1 to 0.5% of patients surviving the acute phase of PTE. However, a recent report noted that CTEPH occurred in 3.8% of patients with a history of acute PTE. Physicians should be aware of the risk of progression to CTEPH when treating patients with acute PTE.

In Japan, the Specific Disease Respiratory Failure Study Group of the MHLW established criteria for the diagnosis of CTEPH and conducted a nationwide survey in 1997. The number of patients with CTEPH was estimated to be 450 (95% confidence interval: 360 to 530). The MHLW then designated CTEPH a specific disease and has conducted an annual epidemiological survey of it. In 2006, a total of 800 patients with CTEPH were provided with medical care certificates for the treatment of a specific disease. Assessment of case reports on 520 of the 800 patients with CTEPH revealed that female patients were predominant, with a female to male ratio of 2.8:1, and that the mean age of patients was 62±13 years. Female patients were predominant, especially among those over 40 years of age, with no gender difference observed in younger patients.

#### 3 Etiology

The mechanisms of onset of CTEPH are still uncertain. In Europe and the United States, CTEPH is considered a chronic condition occurring in patients with a history of acute PTE caused by DVT. In a nationwide survey in Japan, only 28% of patients with CTEPH had DVT. Although some patients with CTEPH had known risk factors for DVT, such as coagulopathy (such as presence of antiphospholipid antibodies and deficiency of antithrombin, protein C, or protein S), heart disease, and malignant tumors, 43.9% of patients assessed had no apparent underlying conditions. Frequencies of human leukocyte antigen (HLA)-B*5201 and HLA-DPB1*0202 were high among patients with a particular type of CTEPH, and in patients carrying HLA-B*5201 and/or -DPB1*0202, the frequency of DVT was significantly lower than in other patients. These findings suggest that there may be a different mechanism of onset of CTEPH in the Japanese population not shared by Western populations. Some patients with CTEPH may remain asymptomatic for several months to years following a period with findings suggestive of acute PTE. This asymptomatic period is referred to as a “honeymoon period.” Although the mechanism of latent progression of PH is unknown, several hypotheses, including repetition of latent thrombosis and progression of thrombosis in the pulmonary arteries, have been suggested. Recently, the involvement of small vessel disease in the pathogenesis of CTEPH has been hypothesized.

#### 4 Clinical Manifestations

Although there are no symptoms specific to CTEPH, almost all patients experience exertional dyspnea. Abrupt dyspnea and chest pain develop repeatedly in patients with repetitive CTEPH, while exertional dyspnea becomes severe over time in patients with latent CTEPH without apparent recurrence. Other symptoms such as chest pain, dry cough, and syncope, may develop as well, and bloody sputum and fever may develop in patients complicated by pulmonary bleeding and pulmonary infarction. Patients with right heart failure due to PH may exhibit abdominal distension, body weight gain, and edema of the lower legs.

#### 5 Diagnosis

The diagnosis of CTEPH is made according to the criteria for diagnosis of idiopathic chronic PTE with PH described below. Contrast multi-slice computed tomography (termed multi-slice CT [MSCT] or multi-detector CT [MDCT]) is useful in the diagnosis and differential diagnosis of CTEPH. However, pulmonary angiography is required to determine whether surgery is indicated.

#### 6 Prognosis

According to a report by Riedel et al and the results of a survey of CTEPH in Japan, the prognosis of patients with a mean pulmonary arterial pressure during the stable period of ≥30mmHg is poor.
Table 3. Risk factors for Deep Vein Thrombosis

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Demographics/ environment</th>
<th>Pathology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>Prolonged sitting: During trips and during disasters</td>
<td>Trauma: Leg fractures, leg palsy, spinal injuries</td>
<td>Surgeries: Orthopedic surgery, neurosurgery, abdominal surgery</td>
</tr>
<tr>
<td>Trauma</td>
<td>Acquired hypercoagulability: Coagulation inhibitor deficiencies</td>
<td>Varicose veins of lower limbs</td>
<td>Drugs: Female hormone, hemostatics, corticosteroids</td>
</tr>
<tr>
<td>Malignant tumors</td>
<td>Acquired hypercoagulability: Following surgery</td>
<td>Dehydration/polycythemia</td>
<td>Catheter test/intervention</td>
</tr>
<tr>
<td>Congenital hypercoagulability: Coagulation inhibitor deficiencies</td>
<td>Heart failure</td>
<td>Obesity, pregnancy, postpartum status</td>
<td>Management of severe patients, postoperative patient management, patients with cerebrovascular disorders</td>
</tr>
<tr>
<td>Inflammatory bowel disease, antiphospholipid syndrome, vasculitis</td>
<td>Varicose veins of lower limbs</td>
<td>Congenital iliac bands and webs, iliac compression by the iliac artery</td>
<td></td>
</tr>
<tr>
<td>Vanicose veins of lower limbs</td>
<td>Varicose veins of lower limbs</td>
<td>History of venous thromboembolism: Vein thrombosis, pulmonary thromboembolism</td>
<td></td>
</tr>
</tbody>
</table>

3. Deep Vein Thrombosis

1. Definition
The veins of the extremities are classified into superficial veins that lie above the fascia and deep veins that lie under the fascia. Acute venous thrombosis is thus classified as DVT affecting deep veins and thrombophlebitis affecting superficial veins. The manifestations of DVT depend on the location of affected veins. The present guidelines mainly describe DVT in the veins of the pelvis and lower limbs. 

2. Epidemiology
At autopsy, DVT is observed in 24 to 60% of patients who died in hospital in Europe and the United States and 0.8% of those in Japan. In an epidemiological survey, the Venous Disease Survey Committee of the Japanese Society of Phlebology in 1997 reported that DVT occurred in 506 patients per year, while the number of new patients with DVT was estimated to be 14,674 patients/year, ie, 12/100,000 population/year, in a questionnaire survey conducted by the Japanese Society of Pulmonary Embolism Research in 2006. These findings reflect the fact that the incidence of DVT has increased about 30-fold during the last decade. On the other hand, the annual incidence of DVT in Europe and the United States were calculated as 50/100,000 population/year on the basis of reports published between 1976 and 2000. The incidence of DVT in Japan has increased rapidly to about one-fourth those in Europe and the United States.

3. Etiology and Risk Factors
The major causes of venous thrombosis are venous endothelial dysfunction, hypercoagulability, and interruption of venous blood flow. The development of DVT involves these major causes as well as various other risk factors of various strengths, (Table 3). Most cases of DVT in the veins in the neck and upper limbs are iatrogenic, and caused by the placement of an intravenous line, pacemaker catheter, or hemodialysis shunt, and cases of thoracic outlet syndrome are also observed. DVT in the superior vena cava develops in patients with superior vena cava syndrome in whom DVT is typically caused by mechanical compression of this vein by mediastinal tumor. DVT in the IVC often develops as a result of extension of thrombus from veins in the pelvis or lower limb. Cases of IVC filter thrombosis and of Budd-Chiari syndrome are also observed. In the veins in the pelvis and lower limb, DVT may develop as a result of venous compression due to congenital iliac bands and webs in the pelvis, iliocaval compression by the iliac artery, insertion or placement of a catheter into the femoral vein, or bed rest with limited leg movement. Cases of DVT in the lower legs are predominant. DVT in the lower leg often develops in the veins of the soleus muscle, which receive blood from the medial, central, and lateral parts of the lower leg, and the vein running through the central portion of the soleus muscle is largest and the main location of DVT.

4. Pathophysiology
Thrombus in a vein adheres to the venous wall over a period of several days after thrombus formation as a result of inflammatory changes, and then regresses due to organization. Although venous valves included within the lesion may be damaged, some valves maintain function. Blood flow recovers after lysis or regression of thrombi during the acute phase. During the chronic phase, recovery of blood flow occurs after organization or recanalization of thrombi. Thrombi in the popliteal vein and the distal veins disappear almost completely in several days to several weeks, while thrombi in the proximal leg veins remain as fibrotic bands, although about 50% of such thrombi regress within one year after formation. The central edge of thrombus can become embolic or a source of emboli. While white thrombi and mixed thrombi tend to adhere to the venous wall, red thrombi do not adhere to the venous wall tightly and are easily detached from the vascular wall and cause embolism. Thrombus in veins in the pelvis and lower limbs are detached during movement of the hip and knee joints in the supine or sitting position. During walking, thrombi are detached from the wall as a result of calf muscle pump function.

Emboli often...
occur within one week after formation or progression of thrombus, but may recur depending on the amount of movement of the lower limbs and blood flow in the central edge of thrombus.\textsuperscript{47,50} The severity of PTE correlates with the size of emboli and frequency of formation of emboli. Severe PTE is often caused by thrombus in leg veins above the popliteal vein, especially the femoral vein, but may be caused by thrombosis in soleus veins.\textsuperscript{47,49,50} Although the source of emboli is uncertain in 30 to 60% of patients with PTE,\textsuperscript{38,45} autopsy has frequently revealed the presence of new and old sources of emboli in the veins of lower limbs.\textsuperscript{50}

5 Typing and Staging of DVT
DVT in the pelvis and lower limb is classified into central type of DVT (iliac DVT and femoral DVT), which occurs in veins above the popliteal vein, and peripheral type of DVT (lower leg DVT), which occurs in popliteal vein and distal veins. In the present guidelines, DVT is also classified based on clinical signs/symptoms and severity of anomalous venous drainage into acute and chronic phases. Signs and symptoms of acute anomalous venous drainage include swelling, pain, and skin color change in patients with central type of DVT. In patients with iliac DVT with diffuse occlusion, venous necrosis due to poor arterial perfusion develops in the acute phase. It is of practical use to classify the severity of clinical signs/symptoms according to the presence/absence of painful swelling, painful swelling with discoloration (phlegmasia alba dolens [milk leg], phlegmasia cerulea dolens [blue leg]), and venous necrosis.\textsuperscript{38,54} Although peripheral type of DVT typically causes pain, many patients are asymptomatic. Important findings of physical examination include the presence of thrombosed veins or tenderness on palpation (direct findings) and hard lower leg muscles (indirect finding).\textsuperscript{38,54} When DVT recurs during the chronic phase, the patient exhibits signs and symptoms characteristic both the acute and chronic phases of DVT.

6 Prognosis and Recurrence
The short-term prognosis of DVT in the pelvis and lower limb depends on the presence/absence and severity of acute anomalous venous drainage, acute PTE, and arterial embolism. Acute anomalous venous drainage often subsides within several months after onset. Acute PTE is the most serious condition,\textsuperscript{45,55} and requires both primary and secondary prevention. In patients with arterial embolism, the presence/absence of patent foramen ovale must be confirmed.\textsuperscript{56} The long-term prognosis of DVT depends on the presence/absence and severity of post-thrombotic syndrome, recurrent DVT, chronic PTE, and arterial embolism.\textsuperscript{38,45,54} Post-thrombotic syndrome develops in about 40% of patient with central type of DVT,\textsuperscript{57} and is caused by abnormal valves in perforating arteries and superficial veins. When DVT recurs, acute manifestations are observed, and the incidences of PTE and post-thrombotic syndrome are increased.\textsuperscript{58} Early treatment improves the prognosis of patients with DVT. Patients with recurrent DVT following anticoagulation therapy must be assessed for thrombophilia.\textsuperscript{59,60} To ensure prevention of recurrent DVT, patients must continue exercise and compression therapy as well as anticoagulation therapy for an appropriate length of time. The duration of anticoagulation therapy should be determined considering the reversibility of risk factors and whether the condition is idiopathic and/or permanent.\textsuperscript{45,60}

II Descriptions of Individual Diseases

1. Acute Pulmonary Thromboembolism

1 Diagnosis
Accurate diagnosis of acute PTE is difficult, since no physical or laboratory findings are specific to acute PTE. Physicians should suspect acute PTE when the following non-specific findings are present. Acute PTE should be included in the differential diagnosis if patients have dyspnea that cannot be explained by other causes.

![Figure 1](http://www.jcsguidelines.org/pdf/figure1.png)

**Figure 1.** Steps in the diagnosis of acute pulmonary thromboembolism. Start heparin therapy when pulmonary embolism is suspected. Examine for deep vein thrombosis at once. *Screen the patient with chest X-ray, ECG, arterial blood gas analysis, transthoracic echocardiography, and blood chemistry. *When PCPS is not available, maintain circulation with cardiac compression and vasopressors. CT, computed tomography; PCPS, percutaneous cardiopulmonary support. Adapted from Therapeutic Research 2009; 30: 744–747.
(1) Symptoms
The absence of symptoms specific to acute PTE is a major reason for delay or lack of diagnosis of this disease. Its common and major symptoms are dyspnea and chest pain. Typically, such symptoms develop when patients begin walking after bed rest, when they urinate or defecate, or when they change posture.

(2) Clinical Findings
Tachypnea and tachycardia are frequently present. Shock and hypotension may develop as well. DVT may cause swelling of the lower legs and Homans’ sign, etc.

(3) Examinations
Figure 1 illustrates the recommended steps in diagnosis. It should be noted that the flow chart reflects currently available techniques.

[Levels of Recommendations]
1. MSCT, pulmonary angiography, pulmonary scintigraphy, arterial blood gas analysis, D-dimer: Class I
2. Transthoracic echocardiography, magnetic resonance angiography (MRA): Class IIa
3. Transesophageal echocardiography: Class IIb

2 Treatment
(1) Introduction
In the treatment of acute PTE, it should be noted that (1) prompt diagnosis and treatment are essential, since the prognosis after successful treatment during the acute phase is excellent, and that (2) after achievement of stable hemodynamics patients should be carefully followed for recurrence of PTE and should be treated promptly when DVT develop. The main component of treatment of PTE is pharmacological antithrombotic therapy, and anticoagulants and thrombolytics should be used appropriately based on the severity of the patient’s condition. Physicians should also assess whether any DVT remains as soon as possible to consider whether IVC filters are indicated. Figure 2 shows an example of an algorithm of treatment during the acute phase of PTE. It should be noted that this algorithm involves basic concepts and should be modified appropriately according to the condition of individual patients and hospital policies.

(2) Cardiopulmonary Management
The main pathological feature of acute PTE is acute cardio-
Unfractionated heparin should be administered intravenously as an initial bolus dose at 5,000 units, followed by continuous infusion at 1,400 units/hr. Six hours after the initial administration of unfractionated heparin, APTT should be determined for adjustment of the dose according to the above table.

| Dose Adjustment Table for Unfractionated Heparin for Continuous Infusion*1 |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| APTT (sec) | Bolus (units) | Hold (min) | Rate change (mL/hr)*2 | Dose change (units/24 hr) | Repeat APTT |
| <50 | 5,000 | 0 | +3 | +2,880 | 6 hrs later |
| 50 to 59 | 0 | 0 | +3 | +2,880 | 6 hrs later |
| 60 to 85 | 0 | 0 | 0 | 0 | Next morning |
| 86 to 95 | 0 | 0 | –2 | –1,920 | Next morning |
| 96 to 120 | 0 | 30 | –2 | –1,920 | 6 hrs later |
| >120 | 0 | 60 | –4 | –3,840 | 6 hrs later |

*1Use this table for APTT reagents with a therapeutic range of 1.9 to 2.7 times the control.

*2When unfractionated heparin is administered at a concentration 40 units/mL.


### 2) Circulatory Management
Although severity varies depending on the degree of occlusion in the pulmonary vascular bed, patients often exhibit PH, right heart overload, decreased right cardiac output, decreased left cardiac output, and/or shock. Theoretically, treatment should include drugs that have cardiotoxic effects and widen the pulmonary artery.

There is no evidence to recommend volume loading. It has been pointed out that excessive volume loading in the right ventricle may compress the left ventricle and decrease left cardiac output.70 Drug treatment (the drugs of first choice are dopamine and dobutamine;71 norepinephrine72 is effective in patients with hypotension; phosphodiesterase III inhibitors require further evaluation to accumulate clinical data), nitric oxide (NO) inhalation, and other appropriate treatment should be performed.

Patients with cardiopulmonary arrest and those not responding well to drug treatment (patients with progressive hypotension) should be treated promptly with PCPS and be considered for surgical thrombectomy.73,74

### Table 5. Contraindications to Thrombolytic Therapy

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Active internal bleeding</td>
</tr>
<tr>
<td>• Recent spontaneous intracranial bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Major surgery, delivery, organ biopsy or puncture of non-compressible vessels within 10 days</td>
</tr>
<tr>
<td>• Ischemic stroke within 2 months</td>
</tr>
<tr>
<td>• Gastrointestinal bleeding within 10 days</td>
</tr>
<tr>
<td>• Severe trauma within 15 days</td>
</tr>
<tr>
<td>• Neurosurgery or ophthalmologic surgery within 1 month</td>
</tr>
<tr>
<td>• Uncontrolled severe hypertension (SBP &gt;180 mmHg, DBP &gt;110 mmHg)</td>
</tr>
<tr>
<td>• Recent cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>• Platelet count &lt;100,000/mm3, prothrombin time &lt;50%</td>
</tr>
<tr>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Bacterial endocarditis</td>
</tr>
<tr>
<td>• Diabetic hemorrhage retinopathy</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure. Adapted from Guidelines on diagnosis and management of acute pulmonary embolism. Eur Heart J 2000; 21: 1301–1336, with permission from Oxford University Press.

### Table 6. Duration of Anticoagulation Therapy for Patients With Venous Thromboembolism

<table>
<thead>
<tr>
<th>Types of risk factors</th>
<th>Duration of anticoagulation therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients with reversible risk factors</td>
<td>3 months</td>
</tr>
<tr>
<td>• Idiopathic venous thromboembolism</td>
<td>At least 3 months (Determine the duration considering risks and benefits)</td>
</tr>
<tr>
<td>• Congenital coagulation disorder</td>
<td></td>
</tr>
<tr>
<td>• Cancer patients</td>
<td>Long term</td>
</tr>
<tr>
<td>• Patients with recurrent venous thromboembolism</td>
<td></td>
</tr>
</tbody>
</table>


Since mortality is particularly high immediately after the onset of PTE,76 appropriate cardiopulmonary management is quite important.

### 1) Respiratory Management
Patients with acute PTE typically exhibit hypoxemia and hypocapnia (type I respiratory failure).68 Oxygen therapy should be initiated for patients with an partial pressure of arterial oxygen (PaO2) of ≤60 Torr (mmHg) (or a peripheral oxygen saturation [SpO2] of ≤90%).

Nasal cannula, an oxygen mask, or an oxygen mask with reservoir bag should be used as appropriate.

When oxygen therapy does not achieve a PaO2 of ≥60 Torr (SpO2 ≥90%), intubation and mechanical ventilation should be initiated.69 During mechanical intubation, the tidal volume should be set at a low level, 7 mL/kg, to avoid increase in intrathoracic pressure.10
(3) Drug Treatment

1) Initial Treatment
The major components of the treatment of acute PTE are anticoagulation therapy and thrombolytic therapy. The treatment of choice is anticoagulation therapy using unfractionated heparin. This should be performed in all patients unless anticoagulation is contraindicated. When acute PTE is strongly suspected or a long period of time is required to confirm the diagnosis, treatment may be initiated before confirming the diagnosis. Unfractionated heparin should be administered as a single intravenous dose of 80 units/kg or 5,000 units, followed by continuous intravenous infusion at 18 units/kg/hr or 1,300 units/hr. The dose should be adjusted to maintain an activated partial thromboplastin time (APTT) of 1.5 to 2.5 times the control value (Table 4). Infusion of unfractionated heparin should be continued until control of anticoagulation with warfarin is established.

Thrombolytic therapy is performed to promptly improve pulmonary circulation by dissolving thromboemboli, and is also used for the treatment of patients with massive acute PTE with unstable hemodynamics or echocardiography-proven enlargement of the right heart. Montepase, a recombinant tissue plasminogen activator, is the only drug officially indicated for the treatment of acute PTE in Japan. The recommended regimen in adults is intravenous administration of 13,750 to 27,500 units/kg over about 2 minutes. Table 5 lists contraindications to thrombolytic therapy. Although thrombolytic therapy has been proven to be clearly superior to anticoagulation therapy in ensuring prompt dissolution of thrombi and improvement of hemodynamics, no difference in prognosis has been observed in randomized studies of thrombolytic therapy and anticoagulation therapy.

The current criteria for drug treatment for acute PTE are as follows:
(1) Anticoagulation therapy is the treatment of choice for normotensive patients without right heart dysfunction.
(2) Normotensive patients with right heart dysfunction should be carefully assessed for expected benefits and risk of bleeding in considering whether thrombolytic therapy is a treatment option.
(3) Thrombolytic therapy is the treatment of choice for patients with persistent shock and hypotension unless it is contraindicated.

2) Long-Term Treatment
Following treatment with unfractionated heparin, warfarin therapy is used. Warfarin therapy should be initiated during the early phase of treatment with unfractionated heparin, and the dose of warfarin should be adjusted to achieve an optimal prothrombin time and international normalized ratio (PT-INR). The initial dose is 3 to 5 mg in many cases. Warfarin therapy should be continued when the risk of recurrent PTE is higher than the risk of bleeding, and the duration of warfarin therapy will vary depending on the presence and types of risk factors (Table 6). The optimal target range of warfarin therapy is 2.0 to 3.0 PT-INR in foreign countries but is 1.5 to 2.5 PT-INR in Japan because of the risk of bleeding.

[Levels of Recommendations]
Class I
1. During the acute phase of acute PTE, unfractionated heparin should be administered to achieve an APTT of 1.5 to 2.5 times the control value for a period of time until the effects of warfarin are stabilized.

2. Warfarin should be administered during the chronic phase of acute PTE. The duration of warfarin therapy should be 3 months for patients with reversible risk factors and at least 3 months for patients with congenital coagulopathy and those with idiopathic VTE. Warfarin should be administered for a longer period of time to patients with cancer and those with recurrent PTE.

3. In patients with persistent shock, hypotension, and unstable hemodynamics, thrombolytic therapy should be performed during the acute phase of acute PTE.

Class IIa
1. During the acute phase of acute PTE, thrombolytic therapy should be performed in normotensive patients with right heart dysfunction.

Class IIb
1. During the treatment of acute PTE, the dose of warfarin should be adjusted to achieve a PT-INR of 1.5 to 2.5.

(4) Catheter Intervention
Catheter intervention is indicated for patients with acute massive PTE with unstable hemodynamics despite other appropriate treatment. Catheter interventions include catheter-directed thrombolysis (CDT) and catheter fragmentation/ aspiration thrombectomy.

1) Catheter-Directed Thrombolysis
Use of catheters to inject thrombolytics directly to thrombus in the pulmonary arteries is not currently supported. Appropriate methods of injection such as the pulse-spray technique should be used to ensure the efficacy of treatment.

2) Catheter Fragmentation/Aspiration Thrombectomy
Catheter interventions other than catheter-directed thrombolytic therapy include aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy. These techniques are followed by thrombolytic therapy in most cases. It has been suggested that the clinical results of these techniques are comparable to that of surgical thrombectomy. Efficacy evaluation should be based on improvement of hemodynamics and oxygenation, and angiographic findings should not be overemphasized. Physicians should be aware that complications such as injury of vascular walls, peripheral embolism, recurrent thrombosis, traumatic hemolysis, and blood loss may occur.

(a) Aspiration Thrombectomy
The Greenfield embolectomy device has not yet been approved in Japan. Aspiration thrombectomy using guiding catheters for percutaneous transluminal coronary angioplasty (PTCA) has attracted attention because of its simplicity and excellent clinical results. On the other hand, catheters designed to percutaneously remove thrombus from the coronary arteries are not useful in the treatment of acute PTE because of their low suction power.

(b) Thrombus Fragmentation
Thrombus fragmentation is performed to directly break a thrombotic mass in a proximal pulmonary artery and redistribute microemboli into peripheral vessels. Although the thrombi are not recovered, small fragments of a thrombotic mass will respond better to thrombolytic therapy because the total surface area exposed with thrombolytics will be increased significantly. Currently used methods of fragmentation include cutting a thrombotic mass by rotating a pigtail catheter and crushing it with a balloon catheter.
treatment techniques combining fragmentation and aspiration thrombectomy using guiding catheters have been proposed to prevent distal emboli associated with fragmentation, and have achieved excellent results.95

(c) Rheolytic Thrombectomy
Rheolytic thrombectomy is a theoretically safe method since thrombi are removed, but is in many cases ineffective when used alone to treat acute PTE.

[Levels of Recommendations]
1. CT: Class IIb
   The efficacy of simple injection of a thrombolytic agent into the affected pulmonary artery does not differ from that of systemic administration of the drug.
2. Catheter fragmentation/aspiration thrombectomy: Class IIb
   Aspiration thrombectomy
   Thrombus fragmentation
   Rheolytic thrombectomy

(5) Surgical Treatment

1) Indications for Surgery

(a) Treatment Strategies for Acute PTE
When a diagnosis of acute PTE is made, anticoagulation and/or thrombolytic therapy should be promptly initiated. However, since exacerbation of acute PTE may be observed and cardiac arrest may occur during the course of thrombolytic therapy, patients should be carefully monitored and considered for surgery throughout medical treatment. Many reports have indicated that surgical treatment improves the condition of patients with unstable hemodynamics due to massive PTE, and recent surgical techniques may achieve favorable results in patients with massive PTE.96–98 Treatment strategies for patients who develop PTE following surgery should be determined in accordance with the type of surgery and the general condition of patients.

(b) Indications for Surgical Thrombectomy
In patients with circulatory failure or shock due to acute massive PTE causing rapid occlusion of the pulmonary arterial trunk or both right and left main pulmonary arteries, prompt recanalization of the occluded pulmonary arteries is essential.99 Surgical pulmonary thrombectomy under cardiopulmonary bypass is indicated for these patients. In patients without shock, conventional surgical pulmonary thrombectomy is indicated, among other conditions, (1) when tachycardia persists in the absence of hypotension and medical treatment is not effective; (2) when thrombus is observed in the pulmonary arterial trunk or both right and left main pulmonary arteries, and heart failure and/or respiratory failure is rapidly progressive; (3) when thrombolytic therapy is contraindicated; and (4) when free thrombus is present in the right atrium and/or ventricle.100

When post-surgical patients or bedridden patients experience the abrupt onset of circulatory collapse before the diagnosis of acute PTE and medical treatment is not effective, PCPS must immediately be initiated in the ward.101 When such patients are confirmed not to have fatal cerebral complications and are diagnosed with shock due to acute PTE, pulmonary thrombectomy should be performed.

2) Methods of Surgery
Surgical thrombectomy for the treatment of acute PTE involves incision of the affected pulmonary artery to remove thrombus under cardiopulmonary support.102 When poor cardiopulmonary kinetics are observed before surgery, femoral veno-arterial cardiopulmonary support should be initiated promptly as a supportive measure. When shock develops in a patient in the ward, PCPS should be initiated before the patient is transferred to the operating room.

Following median sternotomy, cardiopulmonary support is initiated. An incision is made into the pulmonary arterial trunk and, when necessary, the right main pulmonary artery to remove thrombus. In patients with acute PTE, soft, rod-shaped, relatively fresh red thrombi may be removed. Although thrombus in peripheral arteries should also be removed whenever possible, postoperative thrombolytic therapy is effective in dissolving peripheral thrombus when most central thrombus is removed during surgery. Surgical thrombectomy may be performed during a beating heart procedure. However, when small thrombi are located in many segmental arteries or thrombi are tightly adherent to the vascular wall, thrombectomy should be performed during an arrested heart procedure.

3) Results of Surgical Pulmonary Thrombectomy
Stein et al reviewed 46 reports on 1,300 cases of surgical pulmonary thrombectomy performed from 1985 to 2006, and reported that the mortality of patients undergoing pulmonary thrombectomy was 20%.102 According to annual reports by the Japanese Association for Thoracic Surgery, a total of 539 patients with acute PTE underwent surgical pulmonary thrombectomy during the 7-year period between 2000 and 2006, and the in-hospital mortality was 21.2%. The results in Japan are similar to or better than those in foreign countries. The results are fairly good given the severe condition of patients. During the period between August 1996 and October 2006, the Japanese Society of Pulmonary Embolism Research conducted a survey in 60 institutions in Japan, and a total of 32 patients who underwent pulmonary thrombectomy for the treatment of acute PTE were registered.103 Mean age was 57±17 years, and 21 patients (66%) were female. The initial presentation was shock in 23 patients, cardiopulmonary arrest in 3 patients, and syncope in 11 patients. Underlying conditions included trauma in 3 patients, malignant tumors in 3 patients, cerebrovascular disorder in 3 patients, heart disease in 1 patient, central line placement in 2 patients, and pregnancy in 1 patient. Acute PTE developed after surgery in 13 patients and during prolonged bed rest status in 8 patients. Seventeen patients were inpatients when PTE developed. Before surgical pulmonary thrombectomy, thrombolytic therapy was performed in 10 patients and catheter interventions for pulmonary embolus in 4 patients. Ten patients underwent PCPS before surgery. Six patients (18.8%) died in hospital, and 3 patients (30%) under PCPS died. IVC filters were used in 16 patients (50%).

[Levels of Recommendations]
1. Surgical pulmonary thrombectomy under cardiopulmonary bypass in patients with acute massive PTE with circulatory collapse: Class I
2. Surgical pulmonary thrombectomy for the treatment of acute massive PTE in patients without shock: Class IIa

(6) Inferior Vena Cava Filters
Although the indications for and efficacy of IVC filters have yet to be fully determined and demonstrated, IVC filters have
been increasingly recognized as effective in preventing PTE and its complications.164–106

1) Indications of Permanent IVC Filters107,108
Class I: Among patients with VTE,
Those who are contraindicated for anticoagulation therapy
Those who exhibit treatment-related complications and adverse drug reactions to anticoagulation therapy
Those with recurrent VTE during adequate anticoagulation therapy
Those who are unable to continue anticoagulation therapy

Class IIa: Among patients with VTE,
Those with venous thrombosis in intrapelvic veins or branches of the IVC
Those with large free thrombi in proximal veins
Those undergoing thrombolytic therapy or thrombectomy for the treatment of PTE
Those with VTE with poor cardiopulmonary reserve
Those with recurrent PTE following placement of filters
Those with high risk of complications related to anticoagulants (such as ataxia and frequent falls)
Those undergoing PEA for the treatment of chronic PTE

Class IIb: Among patients without VTE,
Those with trauma associated with a high risk of VTE
Those undergoing surgery with a high risk of VTE
Those with other conditions associated with a high risk of VTE

Class III:
 Patients with acute PTE with neither right heart failure nor DVT who are undergoing anticoagulation therapy
 Patients with peripheral type of DVT who are undergoing anticoagulation therapy
 Contraindications:
 Patients with no access to the vena cava
 Patients without space to place a filter

*Use of a non-permanent IVC filter may be considered for patients with conditions for which an IVC filter will no longer be required after several weeks.

2) Indications for Non-Permanent IVC109–111
Class I: None
Class IIa:
Patients indicated for the placement of a permanent IVC filter but who need the filter for only several weeks to prevent acute PTE.

Class IIb:
Long-term placement of removable filters

Class III:
Patients with acute PTE with neither right heart failure nor DVT who are undergoing anticoagulation therapy
Patients with peripheral type of DVT who are receiving anticoagulation therapy

*Since permanent placement of IVC filters increases the risk of venous thrombosis, removable IVC filters should be removed whenever possible.

[Levels of Recommendations]
The indications for permanent and non-permanent IVC filters are listed as above.

2. Chronic Pulmonary Thromboembolism

1 Diagnosis
Diagnosis of idiopathic chronic PTE with PH (CTEPH) as a condition requiring treatment should be made according to the criteria for diagnosis provided by the Specific Disease Respiratory Failure Study Group of the MHLW (Table 7). CTEPH should be suspected in patients with exertional dyspnea. Patients in whom CTEPH is suspected should be identified based on the typical symptoms and clinical findings listed in Table 7. Arterial blood gas analysis should be performed not only in patients with abnormal chest X-ray findings but also in those with no remarkable X-ray findings. Patients with hypoxemia associated with hypocapnia should be assessed with ECG, echocardiography, and pulmonary function tests to exclude other cardiopulmonary diseases and to confirm the presence/absence of findings of right heart overload such as right ventricular enlargement and right ventricular hypertrophy. In making the diagnosis of CTEPH, physicians should confirm that (1) pulmonary ventilation/perfusion scintigraphy has revealed maldistribution of pulmonary blood flow without abnormal ventilation distribution that has persisted for ≥6 months; or the patient exhibits at least one of the five typical findings of pulmonary artery angio-raphy,112 ie, (a) pouch defects (the presence of round pouch-like shadows of thrombi that have been smoothed by blood flow, (b) webs and bands (band-like stenosis with pulmonary recanalization associated with organization of thrombi, (c) intimal irregularities, (d) abrupt narrowing, and (e) complete obstruction; and (2) right heart catheterization reveals normal pulmonary artery wedge pressure and a mean pulmonary arterial pressure of ≥25 mmHg. Cardiac catheterization is useful for measurement of pulmonary vascular resistance to determine prognosis.

Although contrast CT (MSCT) has been reported to be useful in the diagnosis of CTEPH,113 pulmonary angiography is required to assess the condition of subsegmental arteries and to determine whether surgery is indicated.114

2 Treatment
CTEPH is treated with medical and surgical therapy, and the results with current methods of PEA are excellent. Only a few reports have described catheter interventions for the treatment of CTEPH; use of them is not expected to become common in the future, if they are used at all.

(1) Medical Treatment
The pathophysiology of CTEPH includes PH due to occlusion of pulmonary arteries by organized thrombi, intractable right heart failure, and hypoxemia. Accordingly, surgical removal of organized thrombi (PEA) is the only radical treatment for CTEPH. However, PEA is limited to the treatment of central type of CTEPH. Patients with peripheral type of CTEPH, those with relatively mild CTEPH who do not need surgery, and those with CTEPH with persistent PH following surgery are treated with medical treatment.

In medical treatment, patients with CTEPH who are not indicated for surgery receive anticoagulants for the treatment of VTE, which is considered the cause of CTEPH, oxygen therapy for hypoxemia, pulmonary vasodilators for PH, and cardiotonics and diuretics for right heart failure, whenever necessary.

1) Anticoagulation Therapy
The prognosis of untreated CTEPH depends on pulmonary hemodynamics. It has been reported that even patients with mild CTEPH may exhibit exacerbation of pulmonary hemodynamics over time.19 Such exacerbation is believed to be caused by recurrent acute PTE, and to involve mechanisms
Chronic pulmonary thromboembolism with pulmonary hypertension is defined as the presence of chronic obstruction of pulmonary arteries due to organized thrombi and pulmonary hypertension causing severe exertional dyspnea.

### (1) Major symptoms and other clinical findings

1. Exertional dyspnea (Hugh-Jones Grade II or more severe) or fatigability has been observed for >3 months.
2. Clinical symptoms typically associated with acute pulmonary thromboembolism (abrupt onset of dyspnea, chest pain, syncope, etc.) have occurred at least once.
3. Clinical symptoms (swelling in the lower limbs and pain) suspected deep vein thrombosis in the lower limbs have occurred.
4. Pulmonary bruit is auscultated over the lungs.
5. Chest auscultation reveals abnormal sounds suggestive of pulmonary hypertension (including at least one of the following four findings: (1) increase in the pulmonary component of the second heart sound, (2) a fourth heart sound, (3) noise at the pulmonary arterial orifice during the diastolic phase, and (4) noise at the tricuspid orifice during the systolic phase)

### (2) Laboratory findings

1. Arterial blood gases
   - Hypoxemia associated with hypocapnia (PaCO$_2$ <35 Torr, PaO$_2$ ≤70 Torr)
   - Increase in AaDO$_2$ (AaDO$_2$ ≥30 Torr)
2. Chest X-ray findings
   - Enlargement of pulmonary artery shadow in hilar region (protruding left second arch or enlargement of right descending pulmonary artery; maximal diameter >18 mm)
   - Enlargement of cardiac shadow (CTR ≥50%)
   - Local differences in pulmonary artery shadows (right vs. left lung, upper vs. lower lung)
3. ECG
   - Right axis deviation and pulmonary P wave
   - R ≥5 mm at V1 or R/S >1, or S ≥7 mm at V5 or R/S ≤1
4. Echocardiography
   - Right ventricular hypertrophy, enlargement of the right atrium and ventricle, and distorted left ventricular shape
   - Doppler echocardiography reveals patterns characteristic of pulmonary hypertension or findings of high right ventricular systolic pressure
5. Lung ventilation/perfusion scan
   - Segmental defects without abnormal ventilation distribution that have persisted or are believed to have persisted for ≥6 months even after thrombolytic or anticoagulation therapy. When findings appear to have persisted, scintigraphy should be repeated 6 months later to confirm the findings.
6. Pulmonary angiography
   - As changes due to chronic thrombi, at least one of five findings, including (a) pouch defects, (b) webs and bands, (c) intimal irregularities, (d) abrupt narrowing, and (e) complete obstruction, is observed.
7. Right heart catheterization
   - Mean pulmonary arterial pressure during the chronic stable phase is ≥25 mmHg.
   - Pulmonary arterial wedge pressure is normal (≤12 mmHg).

### (3) Conditions to be excluded

The following conditions, which may cause pulmonary hypertension or abnormal pulmonary blood flow distribution, should be excluded:

1. Left-sided heart disease
2. Congenital heart disease
3. Cor pulmonale due to ventilatory impairment
4. Primary pulmonary hypertension
5. Pulmonary hypertension due to connective tissue disease
6. Aortitis syndrome
7. Congenital malformation of pulmonary vessels
8. Pulmonary hypertension due to hepatic cirrhosis
9. Pulmonary veno-occlusive disease

### (4) Criteria for diagnosis

All of the following criteria should be met:

1. Submission of a new case
   - The patient should exhibit finding 1) of "Major symptoms and other clinical findings" with or without other clinical findings.
   - The patient should exhibit at least 2 of the four "Laboratory findings" 1) to 4), as well as abnormal findings on either 5) Lung ventilation/perfusion scan or 6) Pulmonary angiography, and abnormal findings on 7) Right heart catheterization.
   - All "Conditions to be excluded" should be differentiated.

2. Renewal of a registered case
   - The patient should exhibit finding 1) of "Major symptoms and other clinical findings" with or without other clinical findings.
   - The patient should exhibit "Laboratory findings" 1) with or without other laboratory findings.
   - All "Conditions to be excluded" should be differentiated.

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PaCO$_2$, partial pressure of arterial carbon dioxide; PaO$_2$, partial pressure of arterial oxygen; AaDO$_2$, alveolar-arterial oxygen difference; CTR, cardiothoracic ratio.

Provided by the Specific Disease Respiratory Failure Study Group of the Ministry of Health, Labour and Welfare.
of formation of thrombus in situ. Accordingly, life-long anticoagulation therapy with warfarin is required for patients with CTEPH. Warfarin is often administered with a target INR of 1.5 to 2.5, which is also recommended for patients with acute PTE.

2) Thrombolytic Therapy
Patients with CTEPH may exhibit rapid progression of disease. When levels of coagulation/fibrinolytic molecular markers such as D-dimer are high during disease progression, thrombolytic therapy may yield improvement. Physicians should be aware of this possibility.

3) Hypoxemia
Although there is no conclusive evidence for it, oxygen therapy is expected to improve both the QOL and prognosis of patients with CTEPH. In Japan, home oxygen therapy (HOT) for patients with PH including CTEPH is covered by the NHI.

4) Treatment of Right Heart Failure
The presence of clinically significant right heart failure is an important determinant of the prognosis in CTEPH. Patients with right heart failure who exhibit pleural effusion, hepatomegaly/abnormal hepatic function, thrombocytopenia, leg edema, or other typical signs/symptoms are treated with conventional regimens for heart failure including bed rest, restriction of water intake, diuretics, and oral cardiotonics. Patients in severe condition also require intravenous administration of catecholamines such as dopamine and dobutamine as well as milrinone.

5) Vasodilatation
Although use of classic vasodilators such as calcium blockers, nitrates, and angiotensin converting enzyme (ACE) inhibitors to treat CTEPH has been attempted, the efficacy of these drugs in patients with CTEPH has not been demonstrated. However, recent studies have evaluated the effects of beraprost and epoprostenol, drugs indicated for pulmonary arterial hypertension, on CTEPH. Open-label studies and placebo-controlled studies of bosentan and sildenafil have revealed that these drugs may significantly improve pulmonary hemodynamics, six-minute walking distance, and brain natriuretic peptide (BNP) level, and so on. The efficacy of regimens combining these drugs has also been reported. However, use of these drugs for the treatment of CTEPH is currently not covered by NHI in Japan.

[Levels of Recommendations]
1. Anticoagulation therapy: Class IIa
2. Oxygen therapy/HOT: Class IIb
3. Vasodilatation for the treatment of PH: Class IIb
4. Cardiotonics and diuretics for right heart failure: Class IIb

2) Surgical Treatment

1) PEA by Lateral Thoracotomy
PEA is almost fully established as a method of treatment of CTEPH. Lateral thoracotomy had been used before PEA by median sternotomy with cardiopulmonary bypass and deep hypothermic intermittent circulatory arrest was established as the standard technique. The indications for PEA by lateral thoracotomy are similar to those for the method by median sternotomy, though this procedure is currently considered for only a limited number of patients.

(a) Surgery
Incision along the fourth or fifth rib is made to approach the pulmonary artery. Dissection is started from the interlobar fissure to expose the segmental arteries. Taping is performed to control back flow of blood from peripheral vessels. Dissection must be performed carefully so as not to injure the pulmonary parenchyma. After administration of heparin, either the right or left main pulmonary artery is clamped without cardiopulmonary bypass to monitor changes over time in pulmonary arterial pressure for about 5 minutes. After confirming that pulmonary arterial pressure does not exceed systemic blood pressure, an incision is made into the affected lobe artery to initiate thromboendarterectomy. The dissecting plane is determined as in the median sternotomy technique. The target organized thrombus and the intima are held and pulled along the direction to each segmental artery without cutting off the thrombus and the intima. Following removal of the thrombus and the intima, the peripheral taping is removed to confirm back flow of blood. The incision over the lobe artery is closed by suturing or using an autologous pericardial patch.

b) Results of Surgery by Masuda et al
Since 1986, Masuda et al have performed PEA by lateral thoracotomy in 16 patients. In all patients, a right lateral thoracotomy incision was used to access the pulmonary arteries. No patients exhibited serious arrhythmia or right heart failure. No patients required emergency cardiopulmonary bypass for the treatment of hypoxemia. Two patients underwent thromboendarterectomy by left lateral thoracotomy as a second-stage procedure in a two-staged operation. Two patients (12.5%) died of surgical complications, due to postoperative pneumonia and postoperative pulmonary edema in one case each. The patients who survived surgery exhibited prompt improvement in mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance, and gradual improvement in PaO2 over time, resulting in significant improvement 6 months after surgery. Three patients died 4,220, 1,891, and 1,173 days after surgery, due to sudden death in 2 patients and heart failure in 1 patient. Relationships were suspected to exist between these late-phase deaths and CTEPH.

c) Summary
Median sternotomy, which enables PEA in both right and left pulmonary arteries in one stage, is used as the standard procedure for treatment of CTEPH, and has yielded favorable results, particularly in patients with central type of CTEPH. The lateral thoracotomy technique should be considered only for patients with predominantly unilateral disease with peripheral pulmonary lesions.

[Levels of Recommendations]
1. PEA by lateral thoracotomy: Class IIb

2) PEA With Deep Hypothermia

(a) Indications for Surgery
Findings of various examinations including pulmonary angiography, MSCT, pulmonary perfusion scintigraphy and right heart catheterization are important in determining treatment strategies for CTEPH. Daily et al reported that surgical treatment of CTEPH is indicated for patients with a pulmonary vascular resistance of ≥2300 dyne·sec·cm⁻⁵ in whom pulmonary angiography reveals occlusive lesions of the lobe arteries, while Jamieson et al described this technique as indicated for patients with (1) a mean pulmonary arterial
pressure of ≥30 mmHg and a pulmonary vascular resistance of ≥300 dyne·sec·cm⁻⁵; (2) central edges of thrombi located in surgically accessible areas; and (3) without serious complications. Important determinants of the use of surgery for the treatment of CTEPH are the configuration of occluded pulmonary arteries and clinical manifestations (New York Heart Association [NYHA] Class III or higher without shock). In terms of configuration of affected pulmonary arteries, surgery is indicated for patients with central type of CTEPH that affects central pulmonary arteries including the main pulmonary artery, interlobar arteries, and segmental arteries and causes mural thrombi and intimal hyperplasia, while effective surgical treatment may not be possible in patients with peripheral type of CTEPH affecting peripheral portions of segmental arteries and subsegmental arteries. Appropriate selection of patients is thus important.

(b) Surgical Techniques
Unlike acute PTE, the thrombi in CTEPH are pale white, and organized thrombi are attached firmly to the pulmonary arterial wall. During surgical treatment of CTEPH, organized thrombi must be removed together with the intima. The San Diego group including Daily et al. and Jamieson et al. developed a technique termed PEA in both lungs, which involves a median sternotomy with cardiopulmonary bypass and deep hypothermic intermittent circulatory arrest. PEA is the standard surgical technique for the treatment of CTEPH, since CTEPH usually develops in both lungs; the right and left lungs can be approached simultaneously; cardiac lesions complicated by CTEPH can be treated; and the risk of pulmonary bleeding due to thoracotomy is low.

a) Important Aspects of PEA
Techniques to remove thromboemboli alone without removing the intima are completely ineffective in the treatment of CTEPH. In removing the intima, it is important first to determine the dissecting plane appropriately. Optimally, the dissecting plane should be located between the internal elastic membrane and the media. Second, since organized thrombi are hard and not fragile, the target thrombus and intima should be slowly peeled peripherally to the segmental arteries by pulling the thrombus to remove the tree-like organized thrombus with intima. Third, it is important to ensure a blood-free surgical field. Jamieson stripers are useful for this purpose, and intermittent circulatory arrest should be performed as appropriate. The duration of circulatory arrest should be ≤15 minutes each time. When venous oxygen saturation is decreased to 90%, reperfusion should be performed for at least 10 minutes before restart of circulatory arrest. Major challenges of PEA include the treatment of peripheral occlusive lesions for which surgical thromboendarterectomy cannot be performed by median sternotomy and treatment of patients with fragile mural thrombi for which traction during dissection is difficult to perform.

b) Procedures for PEA
a. Presurgical preparation: In patients with DVT and those with a history of it, an IVC filter is placed before PEA. During surgery, patients should be monitored for deep body temperature (pharyngeal temperature), arterial pressure, and pulse oximetry. Transesophageal echocardiography and Swan-Ganz catheter placement are performed. Endotracheal tubes are placed in the right and left bronchi to prepare for pulmonary bleeding, and ice bags to wrap the head are also prepared. Autologous blood recovery systems (Cell Saver) are used during surgery.

b. Following a median sternotomy, cardiopulmonary bypass is performed with venous drainage from the superior vena cava (directly) and the IVC (through the right atrium) and arterial return to the ascending aorta. When ventricular fibrillation occurs after the initiation of cooling, a left atrial vent is inserted from the right upper pulmonary vein.

c. Under hypothermia, the superior vena cava is freed completely from the right atrium to the innominate vein. The frontal surface of the right main pulmonary artery is exposed to the right superior pulmonary vein, and the left main pulmonary artery to the pericardial reflection.

d. PEA of the right pulmonary artery: A retractor is placed between the superior vena cava and the ascending aorta, and a vertical incision of the right pulmonary artery is made from level of mobilized aorta, past right upper lobe branch, and into the right lower lobe artery. On the posterior wall, a dissecting plane is developed to start PEA. In patients with thrombus in the main pulmonary artery, the dissecting plane can be identified at the site of incision. Under hypothermia to a deep body temperature of 18°C and intermittent circulatory arrest, PEA is performed distally to each segmental artery using a Jamieson stripper. Following PEA, the right pulmonary artery is closed by double running suture with monofilament material.

e. PEA of the left pulmonary artery: Using a heart net, the heart is tugged to the lower right-hand side, and the left pulmonary artery is exposed from the pulmonary trunk to the pericardial reflection. The dissecting plane is developed, and PEA is performed to each segmental artery under intermittent circulatory arrest. Following PEA, the left pulmonary arterial wall is sutured and closed.

f. When an atrial septal defect is present, it is closed. When coronary artery bypass grafting (CABG) or surgical treatment of valvular disease is required, it is performed during rewarming. Since tricuspid valve regurgitation is improved when pulmonary arterial pressure is decreased, no surgical treatment for it is required, in principle.

g. Following rewarming, withdrawal from cardiopulmonary bypass is attempted. The patient can be safely withdrawn from cardiopulmonary bypass when mean pulmonary arterial pressure is 30 mmHg or less. However, when pulmonary arterial pressure is identical to systemic blood pressure or when severe bleeding from the respiratory tract is observed, PCPS is introduced before withdrawal from cardiopulmonary bypass, and protamine is administered thereafter.

h. Cardiac tamponade due to pericardial effusion may occur during the several weeks after surgery. To prevent it, pericardial fenestration is performed on the left side, and a drainage tube is inserted into the left thoracic cavity.

c) Postoperative Management
When a patient with PCPS has returned to the intensive care unit (ICU), withdrawal from PCPS is attempted over 2 to 3 days. Pulmonary edema and endotracheal bleeding due to reperfusion injury are important postoperative complications requiring careful attention. When prolonged respiratory failure develops, the patient should be carefully ventilated using positive end-expiratory pressure (PEEP) for a sufficient length of time. After the risk of respiratory tract bleeding or bloody drainage is decreased, the patient should begin heparin therapy and then be switched to oral warfarin. When PH persists, long-term management of right heart failure with vasodilators (eg, prostaglandin [PG] E, and PGI₂) and catecholamines is required.
Figure 3. Algorithm for diagnosis of deep vein thrombosis. CT, computed tomography; MRV, magnetic resonance venography.

(c) Results of Surgical Treatment
The operative mortality of patients undergoing PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest for the treatment of CTEPH were 11.7% (12/103) and 12.6% (16/127) in the case series reported by Duly et al., 8.7% (13/150) and 5.1% as reported by Jamieson et al., 10.1% (7/69) by Tscholl et al., 10% (66/100) by Thistlethwaite et al., and 4.7% (52/1,100) by Bonderman et al., 8.0% (7/88) by Ogino et al., and 8.3% (7 out of 84 patients undergoing elective PEA) by Ando et al. The results of PEA have recently improved. Although the long-term results of medical treatment of CTEPH are not favorable, PEA is expected to improve cardiopulmonary hemodynamics and to yield a favorable long-term prognosis. It has been reported that the 6-year and 5-year postoperative survival rate were 75%, 86%, respectively, and so on. In the patients with persistent PH following surgery, long-term results are poor.

(d) Summary
CTEPH does not respond to medical treatment. PEA is quite effective in the treatment of central type of CTEPH. PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest, which is performed increasingly often now, significantly improves pulmonary hemodynamics and pulmonary gas exchange, and is associated with favorable results. However, patients with peripheral type of CTEPH should be carefully evaluated to determine whether this surgery is indicated for them.

[Levels of Recommendations]
1. PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest for the treatment of central type of CTEPH: Class I
2. PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest for the treatment of peripheral type of CTEPH: Class IIa

Figure 4. Diagnosis of deep vein thrombosis in the lower limbs by venous ultrasonography.

3. Deep Vein Thrombosis

1 Diagnosis
Diagnosis and treatment of DVT should always be performed considering the risk of PTE (Figures 1, 2). Patients in the acute phase should be evaluated for the presence and location of thrombosis, the characteristics of possible sources of emboli, and the severity of venous insufficiency in selecting appropriate treatment strategies. DVT should be suspected on the basis of the history and physical examination signs/symptoms, and the presence/absence of known risk factors. Patients suspected to have acute-phase DVT should be evaluated with appropriate imaging techniques that enable the presence of DVT to be promptly determined. Noninvasive venous ultrasonography is the examination of choice for evaluation of DVT in the extremities. Minimally invasive contrast CT or magnetic resonance venography (MRV) should be performed to evaluate patients suspected to have abdominal or chest DVT. When the presence/absence of DVT cannot be confirmed with the above techniques, invasive contrast venography should be performed. Differential diagnosis may be performed by quantitative assay. D-dimer can be used for patients in whom the possibility of acute-phase DVT is low. Patients with abnormal D-dimer levels should be evaluated with imaging techniques to confirm the diagnosis. Physicians should be aware that the presence of normal D-dimer levels can exclude acute-phase DVT but cannot exclude chronic-phase DVT. Appropriate imaging techniques should be used to exclude thrombosis. Prior to treatment, the causes of DVT should be investigated.

2 History and Present Illness
During the history and physical examination, physicians should look not only for the symptoms of acute-phase DVT but also those of PTE and arterial embolism. Acute-phase DVT should be suspected when swelling, pain, or color change of the extremities is present. Central type of DVT should be suspected when unilateral swelling is noted. Central type of DVT is suspected in patients with femoral pain, while central or peripheral type of DVT is suspected in patients with lower leg pain. Central type of DVT is suspected when red purple skin is observed in the femoral region or lower leg. Patients with peripheral type of DVT are often asymptomatic. Physicians should suspect peripheral type of
DVT when patients present with dyspnea and/or chest pain. Patients should be evaluated for common known risk factors of DVT (Table 3).

(3) Medical Examination
Patients should be inspected visually for color change and swelling in the extremities, and the extremities should be palpated for pathological changes in the deep veins and muscles.\textsuperscript{38,54,142} Central type of DVT should be suspected when color change or swelling is present in the extremities. The presence of palpable thrombotic veins in the groin is a direct finding of central type of DVT in the lower limbs. Stiff muscles in the lower legs are an indirect finding of central type of DVT, while tender muscles in the lower legs are a direct finding of central or peripheral type of DVT. Central type of DVT should be strongly suspected when patients exhibit skin color change and swelling as well as stiffness and/or tenderness of the lower leg muscles.\textsuperscript{38,142} Severe central type of DVT should be strongly suspected when dermal necrosis of the lower legs as well as skin color change and swelling of the legs are present. A lower leg arterial Doppler test should then be performed to evaluate blood flow in the leg arteries. Patients in whom acute DVT recurs during the chronic phase of DVT exhibit findings of both chronic and acute DVT.

(4) Laboratory Examinations

1) Quantitative Examinations
Quantitative examinations are used for differential diagnosis of DVT on the basis of blood chemistry findings and blood flow. D-dimer is the most important item in screening for DVT. Blood flow is evaluated with ultrasonography, which can determine vessel blood flow, and plethysmography, which can determine blood flow in the lower limbs. Among ultrasonographic techniques for diagnosis of DVT, continuous wave Doppler is used to check for arterial perfusion disorder, while color Doppler and pulsed Doppler are used to check for occlusion and resumption of blood flow.\textsuperscript{38,142} Air plethysmography is commonly used to evaluate lower limbs vein function.

2) Imaging Techniques
Imaging techniques such as ultrasonography,\textsuperscript{151} contrast CT,\textsuperscript{152} MRV, and venography are used to confirm the morphological diagnosis of DVT. During lower limb venous ultrasonography (Figure 4), the following four steps of investigation should be performed: (1) determination of the presence/absence of thrombus in lower limb veins; (2) when thrombus is detected, evaluation of its characteristics to stage disease; (3) when acute-phase DVT is present, determination of the extent of thrombus to determine the type of DVT; and (4) examination of the central edge of the thrombus to evaluate it as a potential source of emboli. Staging should be performed based on comprehensive evaluation of noncompressing veins, brightness of thrombus, and perfusion defects, among other findings\textsuperscript{142} (Table 8). Although venous ultrasonography is a highly reliable technique for diagnosis of acute-phase DVT, it is of limited use in the diagnosis of chronic DVT. On contrast CT, the diagnosis of DVT can be made based on findings of venous filling defects. MRV can also provide findings of thrombosis useful in the diagnosis of DVT, though its reliability is less than that of contrast CT. Since venography provides findings of venous filling defects and delineates the border of thrombus, it can be used to diagnose DVT reliably and exclude other possible diseases.\textsuperscript{143,144}

3) Etiological Evaluation
Etiological evaluation includes blood tests to check for tendency of thrombosis such as the presence of thrombophilia and autoantibodies. Coagulation/fibrinolytic markers are useful in the determination of treatment strategies and the prevention of recurrent DVT. Patients should be examined for congenital conditions such as protein S deficiency, protein C deficiency, and antithrombin deficiency as well as for acquired conditions such as decrease in levels of coagulation inhibitors and increase in levels of tissue factors. Antiphospholipid antibodies, which are autoantibodies known to be associated with DVT, should also be tested.

[Levels of Recommendations]
1. D-dimer: Class IIa
2. Venous ultrasonography: Class I
3. MRV: Class IIa
4. Contrast CT: Class I
5. Venography: Class I

2 Treatment

(1) Introduction (Current Concepts)
Whether a thrombus developing in a deep vein will grow or not depends on external factors as well as the balance between the intrinsic and extrinsic coagulation systems and the fibrinolytic system surrounding the thrombus. In order to ensure effective treatment of thrombosis, physicians should understand the effects of mechanical compression of veins such as that in pregnancy/delivery and surgical treatment, effects of tissue factors such as cancer on the coagulation

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Table 8. Diagnosis of Acute and Chronic Deep Vein Thrombosis by Venous Ultrasonography

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Acute phase</th>
<th>Chronic phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vein</td>
<td>Stenosis (compressibility)</td>
<td>Occlusion (noncompressing)</td>
</tr>
<tr>
<td>Distention</td>
<td>Distended</td>
<td>Distended</td>
</tr>
<tr>
<td>Clots</td>
<td>Floating</td>
<td>Fixed</td>
</tr>
<tr>
<td>Regression</td>
<td>Free</td>
<td>Severe</td>
</tr>
<tr>
<td>Consistency</td>
<td>None/moderate</td>
<td>Hard</td>
</tr>
<tr>
<td>Surface character</td>
<td>Soft</td>
<td>Irregular</td>
</tr>
<tr>
<td>Brightness</td>
<td>Smooth</td>
<td>High/middle</td>
</tr>
<tr>
<td>Homogeneity</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Blood flow</td>
<td>Defect</td>
<td>Total</td>
</tr>
<tr>
<td>Recanalization (in thrombus)</td>
<td>Absent</td>
<td>Partial</td>
</tr>
<tr>
<td>Collateral (in branch)</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

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system, and abnormality or deficiency of regulatory proteins such as proteins C and S and antithrombin (Class I). The optimal method of treatment of DVT involves a combination of techniques to prevent the development of PTE, eliminate or dissolve venous thrombus promptly, and prevent recurrence of thrombosis, maintain the patency of veins, and preserve the function of venous valves. Physicians must consider the clinical severity and natural course of DVT in selecting drug treatment, catheter interventions, and/or surgical thrombectomy, among other techniques (Class IIa).

(2) Drug Treatment
Heparin and warfarin are the essential components of anticoagulation therapy for patients with DVT (Class I).\(^\text{7,8,155,156}\)

Since the anticoagulative effect of unfractionated heparin, which is used in Japan, varies between individuals, the effect of heparin should be monitored with APTT and blood heparin concentration. The target APTT in Europe and the United States is 1.5 to 2.5 times the control APTT.\(^\text{7,157-159}\) This level appears appropriate in Japanese patients, as well (Class I). Following initial intravenous administration of 5,000 units of heparin, 10,000 to 15,000 units of heparin should be continuously infused over 24 hours. The dose should be adjusted according to APTT values. When bleeding complications occur, heparin treatment should be suspended or permanently discontinued. Type II heparin-induced thrombocytopenia (HIT) is a serious treatment-related complication associated with arterial thrombosis and DVT caused by immune reactions. When it is suspected, heparin therapy must be discontinued immediately (Class I). Low molecular weight heparin, which is commonly used in Europe and the United States, is not indicated for the treatment of DVT in Japan. However, the indications for low molecular weight heparin have expanded, and the prevention of VTE in patients undergoing total hip replacement, total knee replacement, surgery for hip fracture, or abdominal surgery has recently been added to them.

When warfarin is administered to patients with thrombosis, heparin and warfarin should be combined for 5 days before starting warfarin monotherapy. The dose of warfarin should be adjusted to achieve a PT-INR of 1.5 to 2.5 (target 2.0) (Class IIb). The risk of bleeding complications increases in patients with a PT-INR of ≥2. Patients with de novo DVT with no known risk factors should receive warfarin for 3 to 6 months (Class IIa), while patients with recurrent DVT or long-term risk factors such as cancer, antithrombin deficiency, or antiphospholipid antibody syndrome should receive warfarin as long as the relevant risks continue (Class IIa). Systemic thrombolytic therapy decreases the incidences of DVT and the sequelae of thrombosis (Class IIa).\(^\text{160-163}\) Urokinase (UK) should be infused intravenously at a dose of 60,000 to 240,000 units/day on Day 1 and at tapered doses from Days 2 to 7 (Class IIa).

[Levels of Recommendations]
1. Combined use of of heparin and warfarin in the treatment of acute DVT: Class I
2. Heparin control with a target APTT of 1.5 to 2.5 times the control in the treatment of acute DVT: Class I
3. Warfarin control with a target PT-INR of 2.0 (1.5 to 2.5) times the control in the treatment of acute DVT: Class IIb
4. Systemic thrombolytic therapy in the treatment of acute DVT: Class IIa

(3) Physical Therapy (Exercise and Compression)
During the acute phase of DVT, physicians should carefully consider clinical severity and the natural course of DVT in selecting appropriate treatment such as drug treatment, catheter interventions, and/or surgical thrombectomy, among other techniques. Patients should follow surgical thrombectomy start postoperative physical therapy by wearing elastic stockings and start walking shortly after surgery. Exercise and compression may enhance improvement of swelling and pain and significantly decrease the incidence of sequelae of thrombosis (post-thrombotic syndrome) (Class I).\(^\text{164-166}\)

When treatment of DVT is initiated after the acute phase, its main purpose should be treatment of swelling and pain, prevention of recurrent thrombosis, and prevention of occurrence or worsening of post-thrombotic syndrome. Whether elastic stockings should be used continuously or not should be determined for individual patients based on the degree of improvement of venous function. It is preferable that elastic stockings exerting higher pressures be used continuously for patients with severe symptoms or those with poor venous function.

[Levels of Recommendations]
1. Elastic stockings: Class I

(4) Catheter Interventions (Thrombolysis, Aspiration Thrombectomy, Stenting)
The efficacy of thrombolytic therapy often depends on the timing of treatment and the volume of thrombus. Treatment should be performed as promptly as possible to ensure its success. It is preferable that CDT be initiated during the acute phase of DVT.\(^\text{167,168}\) In the treatment of iliofemoral venous thrombosis, it is difficult to obtain sufficient thrombolysis with CDT with a small dose of UK (240,000 units/day). Some physicians remove thrombi as soon as possible using thrombectomy catheters, and then change catheters to perform CDT.\(^\text{169}\) Aspiration thrombectomy may be combined with CDT in some cases. Endovascular treatment using balloons and stents is expected to improve the outcome of patients who have remaining stenosis following CDT.\(^\text{170,171}\)

Anticoagulation therapy should be performed following CDT to prevent progression or recurrence of thrombosis.

[Levels of Recommendations]
1. CDT: Class IIb
2. Aspiration thrombectomy: Class IIb
3. Venous stenting: Class IIb

(5) Surgical Thrombectomy
Surgical thrombectomy is useful in preventing severe sequelae of thrombosis in otherwise healthy patients and venous necrosis in patients with phlegmasia cerulea dolens (Class IIa), and is indicated for lesions that are not accessible by means of catheters, lesions in which thrombus cannot be sufficiently dissolved, and patients for whom anticoagulation therapy is contraindicated.\(^\text{172}\)

Under general anesthesia, thrombi in the common/external iliac veins are removed using Fogarty embolectomy catheters. Thrombi in peripheral regions should be removed in antegrade fashion with the milking technique and the Esmarch bandage. Some are of the opinion that an arteriovenous fistula should be created. Iliac vein compression should be treated with balloon dilatation and/or stenting. Since blood does not travel backwards when the valves of the external iliac vein are intact, and blood also travels backwards when the common iliac vein is occluded and the internal iliac vein is patent, the presence/absence of remaining thrombus must be determined with...
Table 9. Risk Classification, Incidence of Venous Thromboembolism, and Recommended Preventive Treatments

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Lower leg DVT (%)</th>
<th>Central type of DVT (%)</th>
<th>Symptomatic PE (%)</th>
<th>Fatal PE (%)</th>
<th>Recommended preventive treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.002</td>
<td>Early ambulation and active exercise</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>10 to 2</td>
<td>2 to 4</td>
<td>1 to 2</td>
<td>0.1 to 0.4</td>
<td>Elastic stockings or IPC</td>
</tr>
<tr>
<td>High risk</td>
<td>20 to 40</td>
<td>4 to 8</td>
<td>2 to 4</td>
<td>0.4 to 1.0</td>
<td>IPC or anticoagulation therapy*</td>
</tr>
<tr>
<td>Highest risk</td>
<td>40 to 80</td>
<td>10 to 20</td>
<td>4 to 10</td>
<td>0.2 to 5</td>
<td>(Anticoagulation therapy* plus IPC) or (Anticoagulation therapy* plus elastic stockings)</td>
</tr>
</tbody>
</table>

*Patients undergoing orthopedic surgery or abdominal surgery should receive enoxaparin, fondaparinux, or low-dose unfractionated heparin, while other patients should receive low-dose unfractionated heparin. Patients at highest risk should be treated with adjusted-dose unfractionated heparin (monotherapy) or adjusted-dose warfarin (monotherapy).

Venography and angioscopy during surgery. Following surgery, heparin should be administered for 5 days, and warfarin therapy should be initiated one day after surgery and continued for 6 months. Beginning one day after surgery, patients should wear elastic stockings and walk. When an arteriovenous fistula has been created during surgery, it should be closed 6 weeks after surgery. In order to achieve favorable results, surgery should be avoided whenever possible when ≥7 days have passed since the onset of DVT. Patients with phlegmasia cerulea dolens should be treated with fasciotomy in lower legs to decompress the compartment and improve circulation. Although surgical thrombectomy has yielded favorable short- and long-term results (Class IIa), the number of patients undergoing surgical thrombectomy is small in Japan.

1. Surgical thrombectomy: Class IIb

4. Prevention of Pulmonary Thromboembolism/Deep Vein Thrombosis (Venous Thromboembolism)

1 Evaluation of the Risk of Venous Thromboembolism and Methods of Prevention for Each Risk Level

Primary prevention of VTE is considered mainly for hospitalized patients. The risk of VTE is classified into four levels, ie, low, intermediate, high, and highest (Table 9). Each surgical or disease risk level should be evaluated comprehensively considering additional risk factors (Table 10).

2 Methods to Prevent Venous Thromboembolism

(1) Walking and Active Exercise

Initiation of walking and active exercise during the early postoperative period is essential to prevent VTE. When patients are unable to become early ambulatory, leg raising, massage, and active and passive foot joint exercise should be performed.

(2) Elastic Stockings

During hospitalization, patients should wear elastic stockings before and after surgery as long as the risk of VTE exists. Elastic stockings are beneficial since they do not cause complications such as bleeding, are easy to use, and not expensive.

(3) Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) is beneficial in high-risk patients, especially those with a high risk of bleeding. In principle, IPC should start before or during surgery. When the presence of DVT cannot be excluded prior to initiation of IPC, physicians must obtain informed consent from patients after adequate explanation of the risk of thromboembolism, and should examine patients carefully for PTE. Patients undergoing bed rest should continue IPC all day long. Even after they become ambulatory, patients should use IPC during bed rest until they are able to walk for a sufficient length of time.

(4) Low-Dose Unfractionated Heparin

Unfractionated heparin is administered at a dose of 5,000 units every 8 or 12 hours at least until the patient is able to walk for a sufficient length of time. Physicians should consider switching from heparin to warfarin therapy when the risk of thrombosis persists and the patient requires long-term preventive therapy. The risk of bleeding should be carefully evaluated. Heparin should be administered with special care before and after spinal or epidural anesthesia. Reduction of anticoagulant dose should also be considered during these periods.
Table 11. Classification of Risk of Venous Thromboembolism by Type of Surgery

<table>
<thead>
<tr>
<th>Risk level</th>
<th>Surgery, urology, gynecology</th>
<th>Orthopedic surgery</th>
<th>Obstetrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Non-major surgery in patients &lt;60 years old</td>
<td>Upper limb surgery</td>
<td>Normal delivery</td>
</tr>
<tr>
<td></td>
<td>Major surgery in patients &lt;40 years old</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Non-major surgery in patients ≥60 years old or those with risk factors</td>
<td>Upper limb surgery including bone collection from the ilium or collection of nerve/skin from the lower limbs</td>
<td>Caesarean section (excluding high-risk pregnancy)</td>
</tr>
<tr>
<td></td>
<td>Major surgery in patients ≥40 years or those with risk factors</td>
<td>Spine surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spine/spinal injury</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower limb surgery</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uncomplicated leg injury distal to the femur</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Major cancer surgery in patients ≥40 years old</td>
<td>Hip replacement, total knee replacement, surgery for hip fracture (including the shaft of the femur)</td>
<td>Caesarean section in obese women of advanced age Vaginal delivery in women with a history of VTE or thrombophilia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pelvic osteotomy (eg, Chiari osteotomy of pelvis, acetabular rotational osteotomy)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg surgery in patients with additional risk factors for VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgery for malignant tumors of the lower limb</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe trauma (multiple trauma), pelvic fracture</td>
<td></td>
</tr>
<tr>
<td>Highest risk</td>
<td>Major surgery with a history of VTE or thrombophilia</td>
<td>&quot;High risk&quot; surgery in patients with a history of VTE or thrombophilia</td>
<td>Caesarean section in women with a history of VTE or thrombophilia</td>
</tr>
</tbody>
</table>

Risk level should be determined comprehensively on the basis of the risks of planned surgical procedures and conditions and additional risk factors. For example, when a patient has a strong additional risk factor, risk level should be increased by one rank. Also, when there is more than one weak additional risk factor, risk should be increased by one rank.

Additional factors that increase the risk of VTE: Thrombophilia, history of VTE, malignant disease, cancer chemotherapy, severe infection, central venous catheterization, prolonged bed rest, leg palsy, leg fixation with plaster band, hormone therapy, obesity, varicose veins, etc. (Thrombophilia include antithrombin deficiency, protein C deficiency, protein S deficiency, and antiphospholipid syndrome.) Although there is no strict definition for it, major surgery is basically understood to include all abdominal surgeries and other surgeries that require ≥45 minutes to perform, and should be further classified comprehensively based on the anesthetic techniques, volume of bleeding, volume of transfusion, and length of surgery.

VTE, venous thromboembolism.

(5) Adjusted-Dose Unfractionated Heparin
Adjusted-dose unfractionated heparin is administered to maintain APTT at the upper limit of the normal range. Although this technique is complicated, even monotherapy with adjusted-dose unfractionated heparin is beneficial in highest-risk patients. 183

(6) Adjusted-Dose Warfarin
Warfarin is administered to maintain PT-INR at the target level. In Japan, a PT-INR of 1.5 to 2.5 is recommended.

(7) Low Molecular Weight Heparin and Factor Xa Inhibitors
This technique is convenient, since preventive treatment using low molecular weight heparin and factor Xa inhibitors has stable effects without significant individual differences and these drugs can be administered subcutaneously once or twice a day without close monitoring. The incidence of adverse drug reactions such as thrombocytopenia and osteopenia is low. In Japan, enoxaparin, a low molecular weight heparin product, is officially indicated for patients following total hip replacement, total knee replacement, or surgical treatment of hip fracture as well as after abdominal surgery associated with a high risk of development of VTE. 184 In addition, fondaparinux, the factor Xa inhibitor, is officially indicated for patients following orthopedic surgery of the lower limb or abdominal surgery, which are associated with a high risk of VTE. 185

3 Selection of Methods of Prevention for Patients Undergoing Surgery or Medical Treatment
Table 11 classifies the risk of VTE by type of surgery. Supplemental information is provided as follows.

(1) General Surgery
Although there is no strict definition for it, major surgery is basically understood to include all types of abdominal surgery and other surgeries that require ≥245 minutes to perform, and should further be classified comprehensively based on anesthetic techniques, volume of bleeding, volume of transfusion, and length of surgery. 156 Physicians should determine when anticoagulation therapy will be started based on the condition of individual patients. Preventive treatment may be initiated the evening before the surgery, immediately after initiating surgery, or after surgery, based on the risks of VTE and bleeding.

(2) Urological Surgery
The risk of VTE is low for transurethral surgery, intermediate for pelvic surgery other than as cancer treatment, and high for total prostatectomy and total cystectomy. Prevention of VTE in patients undergoing intra-abdominal urological procedures such as renal surgery should be performed as for patients undergoing pelvic urological procedures. Although there is no strict definition for it, the classification of major urological surgeries including transurethral procedures should be performed in the same fashion as for general surgery.
(3) Gynecological Surgery
Patients undergoing surgery for the treatment of benign disease (laparotomy, transvaginal procedures, laparoscopic procedures) or surgery for malignant disease using techniques commonly used for the treatment of benign disease and those receiving hormone therapy are considered intermediate-risk patients, while patients undergoing radical treatment of pelvic malignant tumors should be considered high-risk patients.

(4) Obstetric Procedures
Pregnant women who remain in bed for long periods of time due to pregnancy complications should be encouraged to perform leg exercise in bed. Pregnant women who must refrain from exercise should wear elastic stockings or use IPC. When pregnant women undergo Caesarean section following long-term bed rest, physicians should consider preoperative screening for VTE. It is preferable that pregnant women with a history of VTE or thrombophilia undergo preventive drug treatment from the first trimester.

(5) Orthopedic Surgery
Anticoagulation therapy may be performed in patients with leg fracture for whom physical preventive treatment is not feasible and who cannot immediately undergo surgery. Based on the incidence of VTE among patients with uncomplicated leg fracture distal to the femur, the risk of VTE is considered intermediate in this patient population. Since DVT may develop immediately after hip fracture, patients should immediately undergo surgery and leave the bed early. It is uncertain whether anticoagulation therapy is appropriate in patients undergoing spine surgery and those with spine injury or spinal injury, since anticoagulation therapy may pose the risk of bleeding. No safe and effective methods of prevention are available for patients with severe trauma and those with pelvic fracture.

(6) Neurosurgery
Patients undergoing craniotomy other than that associated with brain tumor surgery are considered at intermediate risk of VTE, and patients with brain tumor undergoing craniotomy are considered at high risk. Use of high-dose steroids appears to increase the risk. Prevention of VTE through anticoagulation therapy should be initiated after the risk of bleeding complications after surgery has been decreased to an acceptable level.

(7) Medical Field
Physical preventive therapy should be selected for patients contraindicated for anticoagulation therapy, such as those with hemorrhagic cerebrovascular disorder. Patients with myocardial infarction, respiratory failure, severe infection, or inflammatory bowel disease should be considered at intermediate risk of VTE, while patients with palsy due to stroke and those with congestive heart failure should be considered at high risk. Patients in the ICU, who often have multiple risk factors, should undergo prevention of VTE based on individual assessment of level of risk.

[Levels of Recommendations]
1. Early ambulation and active exercise in low-risk patients: Class I
2. Use of elastic stockings by intermediate-risk patients: Class I
3. Use of IPC in intermediate-risk patients: Class Ia
4. Combined use of IPC and anticoagulation therapy in high-risk patients: Class Ia
5. Combined use of anticoagulation therapy, IPC, anticoagulation therapy, and elastic stockings in highest-risk patients: Class Ia

References


Partsch H, Kaulich M, Mayer W. Immediate mobilization on acute venous thrombosis: Analysis of cost effectiveness. JCS Guidelines for Pulmonary Thromboembolism and DVT 2004; 128:


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