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REVIEW

Current Status and Trends in the Treatment of Acute Pulmonary Thromboembolism

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Untreated acute pulmonary thromboembolism (APTE) is associated with high mortality, which is reduced by prompt treatment. Anticoagulation is fundamental in the treatment of APTE and should be initiated from suspicion. The efficacy and safety of novel anticoagulant drugs, such as oral anti-Xa and anti-IIa inhibitors, are topics in the treatment of APTE and are now under investigation. Thrombolytic therapy is a widely accepted treatment strategy for massive APTE, but its use for submassive APTE is controversial. Catheter intervention, percutaneous cardiopulmonary support and surgical embolectomy are also necessary and effective for some patients with APTE. A retrievable inferior vena cava filter is preferred for transient protection against APTE. Some studies have demonstrated the feasibility of outpatient treatment in patients with APTE after risk stratification. (*Circ J* 2011; **75:** 2731–2738)

Key Words: Anticoagulants; Pulmonary embolism; Thrombolysis; Vena cava filter; Venous thromboembolism

Acute pulmonary thromboembolism (APTE) and deep vein thrombosis (DVT) represent the spectrum of the same disease, namely venous thromboembolism (VTE). More than 50% of cases have associated, usually clinically asymptomatic, APTE among patients with proximal DVT.[1] In approximately 79% of patients who present with APTE, DVT can be found in the lower limbs if sensitive diagnostic methods are used.[2]

VTE is an extremely common cardiovascular disease and APTE is the third most frequent cause of cardiovascular death after ischemic heart disease and stroke in Western countries. In fatal APTE, two-thirds of patients die within the first hour after presentation. Approximately 300,000 people in the United States die from APTE,[3,4] but the diagnosis is often not made until autopsy.[5,6] In Japan, APTE occurred in 7,864 patients in 2006. The number of patients has increased 2.25-fold in the past decade, and the incidence of this condition is estimated to be 62 cases/million population.[7] Because the incidence of APTE in the United States is approximately 500 cases/million population, that in Japan in 2006 was approximately one-eighth that in the United States. Factor V Leiden mutation and prothrombin G20210A mutation, which are associated with VTE in Caucasians,[8] have never been found in Japanese people.[9,10] These findings suggest that a racial factor is also involved in the difference in the incidence of VTE.

The clinical presentation of APTE varies widely from asymptomatic to cardiogenic shock and sudden death. The patient's risk of death mainly depends on the presence or absence of hemodynamic instability and the severity of underlying diseases. Early diagnosis is essential for the management of APTE, because prompt treatment is highly effective in improving the prognosis; however, APTE remains a cause of high mortality: 52% from circulatory collapse and 16% from cardiogenic shock.[11]

Pharmacological anticoagulant therapy is fundamental in all patients with APTE to prevent the extension of the clot and recurrence, unless anticoagulation is contraindicated. Recently, fondaparinux, a selective Xa inhibitor, was approved for the treatment of VTE. Furthermore, novel oral selective factor IIa or Xa inhibitors are currently under investigation and could potentially facilitate and improve the treatment of VTE. One of the current topics for anticoagulant therapy is home treatment of APTE.

More aggressive approaches in the acute phase, such as thrombolytic therapy, catheter intervention, percutaneous cardiopulmonary support (PCPS) and surgical embolectomy, are generally aimed at life-saving restoration of flow through occluded pulmonary arteries according to the patient's hemodynamic status. Physicians should also assess as soon as possible whether any DVT remains in order to decide whether inferior vena cava (IVC) filters are indicated.[12]

We discuss the current status and trends in the treatment of APTE.

Anticoagulant Therapy

The landmark randomized trial by Barritt and Jordan, published in 1960, was the first to demonstrate that patients with APTE benefit from anticoagulant therapy.[13] When APTE is strongly suspected, anticoagulation should be initiated before confirming the diagnosis, unless anticoagulation is contraindicated. Initial therapy for APTE patients comprises either subcutaneous low-molecular-weight heparin (LMWH) (not available in Japan) or fondaparinux,[14] or unfractionated hep-

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arin (UFH) given intravenously or subcutaneously.[15,16] Although the dose of intravenous UFH should be adjusted to maintain an activated partial thromboplastin time of 1.5–2.5-fold the control value, LMWH and fondaparinux rarely require laboratory monitoring.

In Japan, the selective factor Xa inhibitor, fondaparinux, was approved in 2011 as an anticoagulant drug for the treatment of VTE, although it was approved in the USA and Europe in 2004. Fondaparinux is a synthetic, highly sulfated pentasaccharide, which has a sequence derived from the minimal antithrombin binding region of heparin. It catalyzes factor Xa inactivation by antithrombin without inhibiting thrombin. Fondaparinux is given once daily subcutaneously at weight-adjusted doses (5 mg for patients <50 kg, 7.5 mg for patients 50–100 kg, and 10 mg for patients >100 kg) without monitoring. Unnecessary monitoring might be convenient in cases of emergency evacuation from places of disaster such as an earthquake. The drug's half-life is 15–20 h. Heparin-induced thrombocytopenia (HIT) is extremely rare when fondaparinux is used and this agent has a very low cross-reactivity with HIT antibodies in vitro.[17]

An open-label trial[18] randomly assigned 2,213 patients with symptomatic APTE to receive either subcutaneous fondaparinux once daily without monitoring, or continuous intravenous UFH. Both medications were transitioned to an oral vitamin K antagonist (VKA) for long-term therapy. The 2 regimens were associated with similar rates of recurrent APTE (3.8% vs. 5.0%), major bleeding (2.0% vs. 2.4%), non-major bleeding (5.7% vs. 8.4%), thrombocytopenia (0.9% vs. 1.2%), and death (5.2% vs. 4.4%).

In a Japanese open-label trial, which enrolled 80 patients with APTE and DVT and with no indication for thrombolytic therapy and an IVC filter, found that weight-adjusted, fixed-dose fondaparinux was associated with rates of recurrent symptomatic VTE (0% vs. 0% at 3 months), recurrent asymptomatic VTE (1.8% vs. 0% at 3 months) and major bleeding (1.7% vs. 0%) similar to those obtained with intravenous UFH.[19]

Fondaparinux is contraindicated in patients with severe renal insufficiency with creatinine clearance <30 ml/min, because it accumulates and increases the risk of hemorrhage. UFH is indicated in patients with severe renal insufficiency. It has not been established whether fondaparinux is effective and safe for massive APTE patients requiring thrombolytic therapy simultaneously. UFH is also preferred in patients for whom thrombolysis is being considered or those with an increased risk of bleeding, because its short-acting effect can be directly reversed with protamine sulfate.

Long-term anticoagulation by oral VKA is necessary to prevent extension of the thrombus and recurrent VTE. Oral VKA administration can usually be started immediately after the diagnosis of APTE, together with UFH, LMWH or fondaparinux. Initial treatment with UFH, LMWH or fondaparinux can only be stopped after the prothrombin time international normalized ratio (PT-INR) has remained within the optimal target range for at least 24 h.[14]

Oral VKA should be administered during the chronic phase of APTE. The duration of VKA therapy should be 3 months for patients with transient risk factors, such as surgery, and at least 3 months for patients with congenital coagulopathy and those with unprovoked VTE.[20,21] Oral VKA should be administered for a longer period of time to patients with cancer and those with recurrent VTE.[22] To determine the optimal duration of anticoagulation for patients with unprovoked VTE, several markers for predicting the risk of recurrence, such as the D-dimer level after cessation of anticoagulation and residual DVT, have been investigated.[23–26]

Novel Anticoagulant Drugs

To date, VKAs are the only available oral anticoagulants approved for the long-term treatment of VTE in the world. VKA have a slow onset of action and a correspondingly slow reversion time to normal.[27] When an immediate anticoagulant effect is needed, administration of parenteral fast-acting anticoagulants (UFH, LMWHs or fondaparinux) is necessary. VKAs have a narrow therapeutic range and their effect needs frequent monitoring with determination of the PT-INR. Metabolism of VKA is affected by genetic factors such as polymorphisms in the CYP2C9 and VKORC1 enzymes. Additionally, VKA have multiple interactions with drugs and diet.

During the past decade, several new oral anticoagulants that more selectively inhibit coagulation factors, such as factor IIa or factor Xa, have been investigated.[28] The major advantages of these drugs are the predictable anticoagulant effect related to the administered dose, and no requirement for laboratory monitoring of their anticoagulant effect. Also, owing to their specificity, fewer clinical drug interactions are expected. Nevertheless, the absence of an appropriate antidote for these drugs and the need to monitor their use in specific circumstances, such as patients with renal impairment, are problems that need to be solved.[28]

Dabigatran, an oral factor IIa inhibitor, was investigated in a randomized, double-blind, non-inferiority trial, the RE-COVER study, in which 2,539 patients with acute VTE were initially given parenteral anticoagulation therapy for a median of 9 days, and then treated for 6 months with either dabigatran (150 mg twice daily) or warfarin (dose-adjusted to achieve PT-INR of 2.0–3.0).[29] The rates of recurrent VTE were 2.4% in the dabigatran group and 2.1% in the warfarin group, respectively (hazard ratio (HR) with dabigatran 1.10, 95% confidence interval (CI) 0.65–1.84). Major bleeding occurred in 1.6% and 1.9% of patients in the dabigatran and warfarin groups, respectively (HR with dabigatran 0.82, 95%CI 0.45–1.48);[29] therefore, a fixed dose of dabigatran seems to be as effective as warfarin for the treatment and prevention of VTE recurrence and has a safety profile similar to that of warfarin.[29]

Rivaroxaban, an oral factor Xa inhibitor, was investigated in an open-label, randomized, event-driven non-inferiority trial, the EINSTEIN study, in which 3,449 patients with acute symptomatic DVT were treated with either oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) (n=1,731) or subcutaneous enoxaparin followed by a VKA (either warfarin or acenocoumarol; n=1,718) for 3, 6, or 12 months.[30] Rivaroxaban had non-inferior efficacy with respect to the primary outcome (36 events (2.1%), vs. 51 events with an enoxaparin-vitamin K antagonist (3.0%); HR, 0.68; 95%CI, 0.44–1.04; P<0.001) (**Figure 1**). The principal safety outcome occurred in 8.1% of the patients in each group.

In parallel, a double-blind, randomized, event-driven superiority study was performed that compared rivaroxaban alone (20 mg once daily) (n=602) with a placebo (n=594) for an additional 6 or 12 months in patients who had completed 6–12 months of treatment for VTE. Rivaroxaban had superior efficacy (8 events (1.3%) vs. 42 with a placebo (7.1%); HR, 0.18; 95%CI, 0.09–0.39; P<0.001) (**Figure 1**). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%) vs. none in the placebo group (P=0.11). A simple, single-drug approach using rivaroxaban is effective and safe for both short-term and continued treatment of VTE.[30]

Edoxaban, which is also an oral direct factor Xa inhibitor,

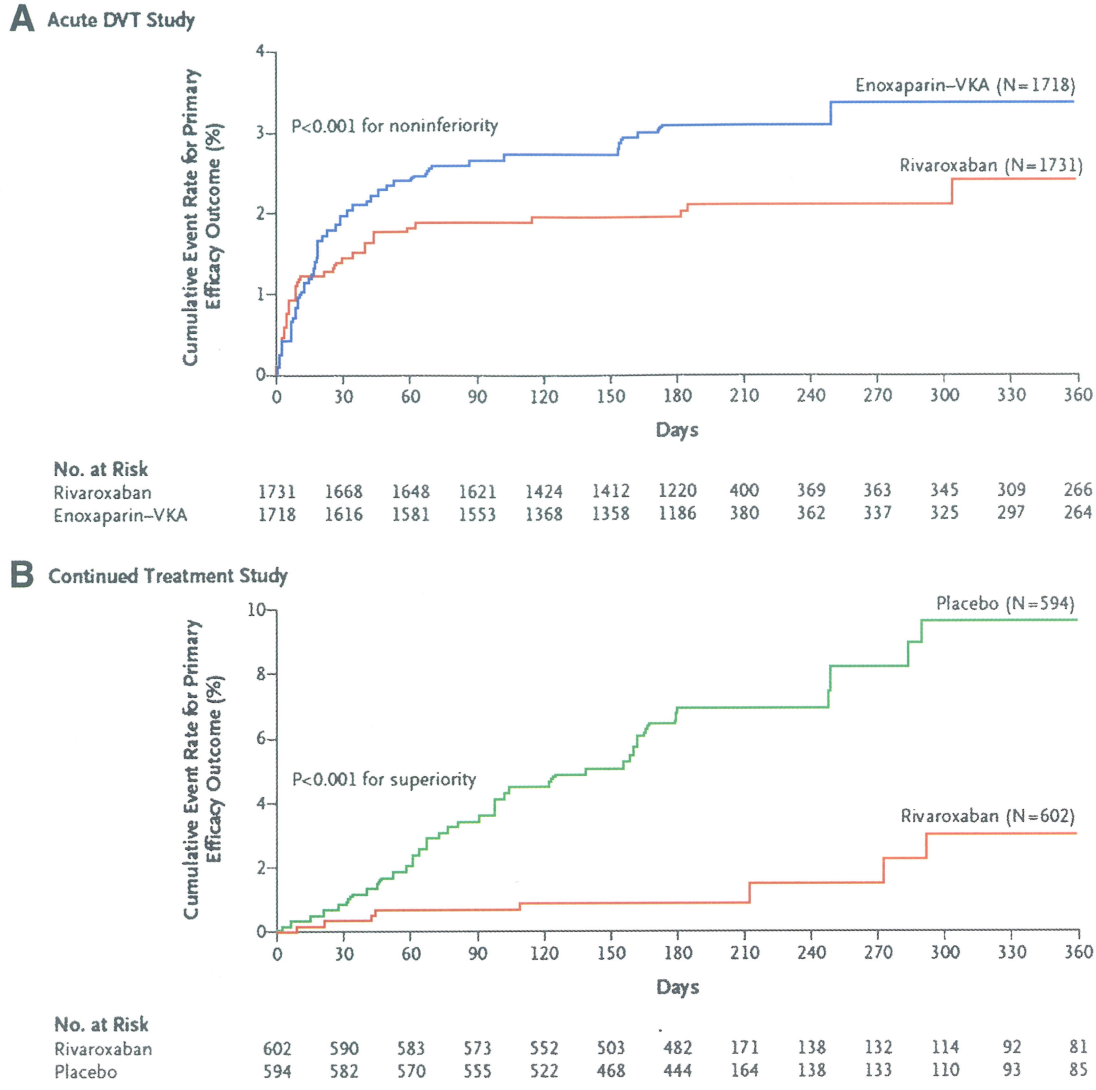

Figure 1. Kaplan-Meier cumulative event rates for the primary efficacy outcome. VKA, vitamin K antagonist. (Modified from EINSTEIN Investigators[30] with permission. Copyright © 2010 Massachusetts Medical Society. All right reserved.)

is currently in phase III evaluation for the treatment of VTE.

Novel anticoagulant agents offer an attractive option for the treatment of VTE and could potentially replace VKA and LMWH in the near future.

Thrombolytic Therapy

Thrombolytic therapy is performed to accelerate clot lysis, restore lung perfusion and decrease right ventricular (RV) overload compared with anticoagulant therapy alone. Although thrombolytic therapy has been proven to be clearly superior to anticoagulant therapy in ensuring prompt dissolution of thrombi and improvement of hemodynamics,[31–36] no difference in prognosis between thrombolytic therapy and anticoagulant therapy alone has been observed in randomized studies, except for one small study.[37]

Thrombolysis is a widely accepted treatment strategy for patients with hemodynamic instability (massive APTE) (Figure 2); however, at present, insufficient evidence exists that hemodynamically stable patients with RV dysfunction on echocardiography or chest CT (submassive APTE) benefit from thrombolysis. The clinical benefit of thrombolysis for submassive APTE is under investigation.[38]

Thrombolytic drugs (urokinase, streptokinase or tissue-type plasminogen activator [t-PA]) are usually administered systemically. Heparin should not be infused concurrently with streptokinase or urokinase, but it can be given during alteplase administration.[39] The greatest benefit is observed when treatment is initiated within 48 h of symptom onset,[40] but thrombolysis can still be useful in patients who have had symptoms for 6–14 days.[41]

Thrombolytic therapy carries a significant risk of bleeding, especially when predisposing conditions or comorbidities exist. Major contraindications to thrombolytic therapy include intracranial disease, uncontrolled hypertension at presentation, and recent major surgery or trauma.[42]

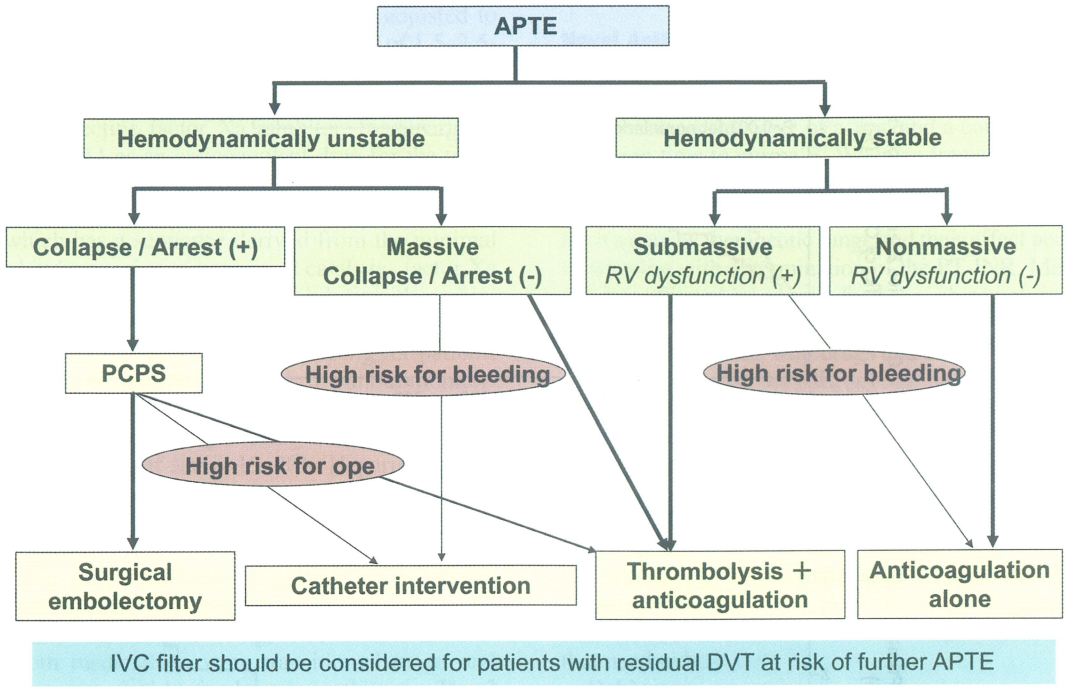

Figure 2. Treatment of acute pulmonary thromboembolism (APTE). DVT, deep vein thrombosis; IVC, inferior vena cava; PCPS, percutaneous cardiopulmonary support; RV, right ventricle.

Catheter Intervention

Percutaneous catheter fragmentation and embolectomy may be considered for massive APTE and the patient has contraindication or failure of thrombolysis (Figure 2). Although the previous reports are limited to case reports and series,[43–46] successful thrombus fragmentation and embolectomy can lead to marked hemodynamic improvement. Complications include hemodynamic deterioration because of distal emboli, perforation of pulmonary vessels and cardiac structures, and cardiac tamponade; therefore, percutaneous catheter fragmentation and embolectomy should be restricted to centers in which adequate expertise is available.

Catheter-directed thrombolysis for APTE is not currently recommended in the guidelines, because a randomized trial demonstrated no significant difference between t-PA peripheral administration and intraarterial administration in the improvement of pulmonary arterial pressure and pulmonary flow from initiation up to 2 h of t-PA treatment.[47] Appropriate methods of injection, such as the pulse-spray technique, should be used to ensure the efficacy of treatment.[48]

IVC Filter

An IVC filter is a useful device to prevent APTE from a clot that has detached from the vein's wall. The primary indications for placement of an IVC filter include contraindications to anticoagulation, major bleeding complications during anticoagulation, and recurrent embolism while the patient is receiving adequate therapy (Table 1).[22] Even if anticoagulation alone is performed in the acute phase of APTE, it cannot completely prevent massive recurrent APTE, a critical complication. An IVC filter might be effective in preventing potentially early fatal recurrence in patients with residual DVT and limited cardiopulmonary reserve;[11,49] however, complications of permanent IVC filters include recurrent DVT in approximately 20% and post-thrombotic syndrome in 40% of patients. IVC occlusion affects approximately 22% of patients at 5 years and 33% at 9 years regardless of the use and duration of anticoagulation.[49–51]

Recently, retrievable IVC filters, which may be left in place permanently or retrieved if patients no longer require vena caval interruption, have become more widely used. These filters are implanted only in the acute phase when a venous thrombus can easily migrate and cardiopulmonary reserve is limited. They can then be removed after thrombus dissolution, decreasing the risk of embolism. Although the indications for the use of these IVC filters have not yet been determined, the decision to use these devices should be based on the severity of RV overload, and the size and ease of migration of the DVT. This type of IVC filter also has the risk of complications such as filter migration, fracture, perforation and DVT recurrence when used as a permanent filter. The FDA and PMDA recommended that physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as protection from APTE is no longer needed. Certain types of retrievable IVC filters can be removed several months after placement, and removal approximately 1 year after placement has also been reported.[52–55] The indications for permanent and non-permanent IVC filters are listed in Tables 1,2.[22] If a permanent IVC filter is inserted and the patient's bleeding risk is acceptable, long-term anticoagulant treatment is indicated.[14]

Table 1. Indications for Permanent IVC Filter

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 APTE 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.
IVC, inferior vena cava; VTE, venous thromboembolism; PTE, pulmonary thromboembolism; PEA, pulmonary endarterectomy; APTE, acute pulmonary thromboembolism; DVT, deep vein thrombosis.
From reference 22 with permission.

Table 2. Indications for Non-Permanent IVC Filter

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 APTE
Class IIb: Long-term placement of removable filter
Class III: Patients with APTE with neither right heart failure nor DVT who are undergoing anticoagulation therapy
Patients with peripheral type of DVT who are receiving anticoagulation therapy

*Because permanent placement of IVC filters increases the risk of venous thrombosis, removable IVC filters should be removed whenever possible.
From reference 22 with permission.
Abbreviations see in Table 1.

Table 3. Changes in the Management of APTE in Japan

Method of management	1994.1–1997.10 (n=309)	1997.11–2000.10 (n=257)	2000.11–2003.8 (n=461)	2003.9–2006.8 (n=655)
Anticoagulation (%)	74	82	92	91
Thrombolytic therapy (%)	50	48	58	41
Catheter intervention (%)	6	6	10	10
Surgical pulmonary thrombectomy (%)	2	3	2	1
IVC filter (%)	18	34	35	45

Information compiled from references 11, 66, and 67.
Abbreviations see in Table 1.

PCPS

Previous reports have shown that PCPS is an effective method for patients with severe massive pulmonary embolism and cardiogenic shock (Figure 2).[56–58] In cases of acute severe hemodynamic instability, catecholamines are required to maintain circulation, and intubated respiratory management is also performed if necessary. If acute circulatory failure cannot be relieved by conventional therapy, PCPS is initiated.[58] The use of PCPS as a bridge to recanalization of occluded pulmonary arteries by pulmonary embolectomy, thrombolytic therapy and/or catheter intervention has become an important option for the management of APTE patients with circulatory collapse and cardiogenic shock.[59,60]

Table 4. Pulmonary Embolism Severity Index

	Points assigned
Age	+1 per year
Male sex	+10
Cancer*	+30
Heart failure	+10
Chronic lung disease	+10
Pulse ≥110 beats/min	+20
Systolic blood pressure <100 mmHg	+30
Respiratory rate ≥30 breaths per min	+20
Temperature <36°C	+20
Altered mental status†	+60
Arterial oxygen saturation <90%‡	+20

Overall point score for a patient is obtained by summing the patient's age in years with the points for every applicable predictor. A score of <66 is risk class I, 66–85 is risk class II, 86–105 is risk class III, 106–125 is risk class IV, and >125 is risk class V.
*History of cancer or active cancer. †Disorientation, lethargy, stupor, or coma. ‡With or without the administration of supplemental oxygen.
(Reprinted from Aujesky D, et al. Outpatient vs. inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet* 2011; **378:** 41–48, Copyright (2011), with permission from Elsevier.)

Surgical Therapy

A limited number of patients who require cardiopulmonary resuscitation or have massive APTE with contraindications or inadequate response to thrombolysis are treated with surgical embolectomy (Figure 2). Following the induction of anesthesia and median sternotomy, cardiopulmonary bypass is initiated. The procedure can be performed off bypass, with normothermia, and without aortic cross-clamping or cardioplegic or fibrillatory arrest. An incision is made in the pulmonary arterial trunk, and, when necessary, the right main pulmonary artery, to remove thrombi. The results of embolectomy will be optimized if patients are referred before the onset of cardiogenic shock. The percentage of APTE patients undergoing surgical embolectomy has been decreasing each year (Table 3).

Outpatient Treatment

Treatment out of hospital with LMWH followed by VKA is commonly accepted for DVT patients without symptomatic APTE.[61,62] Recently, some studies demonstrated the feasibility of outpatient treatment for patients with APTE after risk stratification.

Aujecky et al undertook an open-label, randomized, non-inferiority trial. Patients with symptomatic APTE and a low risk of death (pulmonary embolism severity index (Table 4) category I or II) were assigned to initial outpatient (n=171) or inpatient (n=168) treatment with subcutaneous enoxaparin (≥5 days) followed by oral anticoagulation (≥90 days). In the primary analysis, 1 (0.6%) of 171 outpatients developed recurrent VTE within 90 days compared with none of 168 inpatients, satisfying the criteria for non-inferiority (P=0.011).[63] Only one (0.6%) patient in each treatment group died from non-VTE and non-treatment-related causes within 90 days, and 2 (1.2%) of 171 outpatients and no inpatients had major bleeding within 14 days. The mean length of stay was 0.5 days for outpatients and 3.9 days for inpatients.[63]

Otero et al[64] performed a randomized clinical trial to compare the efficacy and safety of early discharge in patients with acute symptomatic APTE classified as being at low risk of death (based on a low prediction rule score and the absence of RV dysfunction). Patients were randomly assigned to early discharge after 3 days in the hospital or to standard hospitalization. During the 3-month follow-up, the incidence of nonfatal recurrence of APTE and hemorrhagic complications did not differ significantly between the 2 groups; however, the study was terminated early by its data and safety monitoring board because of 2 deaths among 132 patients within 10 days in the early-discharge group (2.8% vs. 0%, P=0.30).

Agterof et al[65] investigated the safety of home treatment of hemodynamically stable patients with APTE (n=152) with low (<500 ng/L) levels of NT-proBNP, who were discharged from the hospital within 24 h of presentation. No deaths, occurrence of major bleeding, or recurrence of VTE occurred in the first 3 months after hospital discharge. During the first 10 days, 7 patients were readmitted; in 3 cases, readmission was necessitated by complaints that could be related to APTE.

According to these data, low-risk APTE can be treated out of hospital, similarly to DVT; however, the level of risk acceptable for outpatient treatment is a current issue that needs to be resolved. An appropriate risk stratification method for outpatient treatment, such as residual DVT, which may detach and cause fatal recurrent APTE, should be established.

Although LMWH was used in previous studies, fondaparinux and the new oral anti-Xa or anti-IIa inhibitors might be demonstrated to be effective and safe as initial outpatient anticoagulant drugs for low-risk APTE in the future.

Conclusion

Untreated APTE is associated with high mortality, but early treatment has been shown to apparently improve the prognosis. The risk of early death is much greater after APTE than after DVT. This difference may justify more aggressive initial treatment for APTE compared with DVT, such as thrombolytic therapy, IVC filter implantation and more intensive anticoagulant therapy. Appropriate treatment should be chosen promptly according to the clinical severity and the risk of complications such as bleeding. Novel anticoagulant drugs could potentially replace VKA for the treatment of APTE in the near future. Outpatient treatment for selected low-risk patients with APTE can safely and effectively be used in place of inpatient treatment after the establishment of an optimal risk assessment method.

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