REVIEW

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# Respiratory Review of 2013: Pulmonary Thromboembolism

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Pulmonary embolism (PE), which can originate as a consequence of deep vein thrombosis (DVT), is the most frequent and potentially fatal venous thromboembolic event. Despite the fact that the incidence of venous thromboembolism (VTE) in Asians is lower than that in the Western populations, a recent epidemiologic study demonstrates an increasing incidence of VTE in the Korean population. Anticoagulants, including low molecular weight heparin (LMWH) and vitamin K antagonist (VKAs), have been the main treatments for PE, however, recently new oral anticoagulants (NOACs) were introduced. We will review how well patients with PE can be managed with the existing anticoagulants and NOACs along with the time span of treatment, which still pose some challenges for clinicians.

**Keywords:** Pulmonary Embolism; Anticoagulants

## Introduction

Pulmonary embolism (PE) is a common disease, representing worldwide a health concern, with an estimated annual incidence of 70 cases per 100,000 individuals[1]. A recent large epidemiologic study shows a 33% lower incidence of venous thromboembolism (VTE) in Asian compared with Western populations[2], but a retrospective study in the Korean population demonstrates a yearly increasing incidence of VTE, including deep vein thrombosis (DVT) and PE from 8.83, 3.91 and 3.74 per 100,000, respectively, in 2004 to 13.8, 5.31 and 7.01, respectively, in 2008 (p=0.0001)[3]. Annual incidences also increased each year, particularly among those over 60 years old[3].

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## Courses of PE

Virchow identified hypercoagulability, vessel wall injury, and stasis as the pathogenic triad for thrombosis[4]. About 25% of patients with VTE have no apparent provoking risk factor, 50% have a temporary provoking risk factor such as surgery, and 25% have cancer[5,6]. More than 80% of pulmonary emboli originate from the deep veins of the leg[7]. The embolus obstructs a pulmonary artery and results in the hemodynamic effects of increased workload on the right ventricle, increased alveolar dead space, bronchoconstriction, and arterial hypoxemia secondary to decline of cardiac output[8]. Clinical PE is associated with an 11% to 23% rate of mortality and therefore treatment of VTE is critical[9]. If treated, most acute symptoms in patients who survive resolve during 2 weeks[10] and the rate of mortality in patient with PE is reduced to 1%[9]. Patients who survive an acute PE are, however, at high risk for recurrence of PE[11]. About a third of patients are left with some residual symptoms, and 2% develop chronic thromboembolic pulmo-

nary hypertension (CTPH) due to remaining arterial obstruction[12].

## Diagnosis of PE

Symptoms observed in patients with PE include sudden-onset dyspnea, chest pain, syncope and hemoptysis[13], but clinical manifestations are frequently absent, making accurate diagnosis difficult[14,15]. To improve clinical prediction in diagnosing PE, Wells[16] developed a score for estimation of the patient's risk of PE[17].

There are several imaging tests to diagnose PE, including ventilation and perfusion scans, spiral computed tomography (CT), and pulmonary angiography. Spiral CT has been shown to be superior to ventilation and perfusion scan for detection and exclusion of PE[18]. It is safer and more available than pulmonary angiogram, which outlines thrombi in the pulmonary arteries with intravenous (IV) contrast medium. The patient's presentation should be correlated with the CT scan. If the data coincide with the CT scan, then clinical decision can be made with the CT scan, otherwise additional testing may be indicated[19]. The widespread use of CT increased the diagnosis of incidental pulmonary embolism, which was reported in 2.6% in a meta-analysis[20].

D-dimer is formed when cross-linked fibrin is broken down by plasmin. Levels are almost always increased in VTE[21,22]. A negative D-dimer can be used for exclusion of PE when the onset of symptoms is very recent (that is, it has a high negative predictive value)[16,17,23]. However, a negative D-dimer with rapid enzyme-linked immunosorbent assay does not exclude PE in more than 15% of patients with a high probability clinical assessment[24]. Because D-dimer levels are commonly increased by other conditions, including age, pregnancy, cancer, trauma, inflammation and recent surgery, an abnormal result has a very low positive predictive value for PE.

## Treatment of PE

Anticoagulants should be administered to patients with PE to prevent fatal outcome and to minimize the risk of recurrent VTE, post-thrombotic syndrome or CTPH[14,15].

The current treatment approach for acute PE, according to the American College of Chest Physicians (ACCP) 9th guidelines recommendations, consists of initial treatment with parenteral anticoagulation (low molecular weight heparin [LMWH], fondaparinux, IV or subcutaneous [SC] unfractionated heparin [UFH]), overlapped with vitamin K antagonists (VKAs) for at least 5 days until the prothrombin time (PT) has been within the therapeutic range for two days[14,25,26]. SC LMWH and fondaparinux do not require IV infusion or laboratory monitoring, whereas IV UFH is preferred if there is shock, severe renal impairment (LMWH and fondaparinux are renally excreted), thrombolytic therapy is being considered, or it may be necessary to reverse anticoagulation rapidly[2]. For long-term treatment of PE, the use of VKAs is recommended for 3 months or longer, depending on whether the PE is attributable to a transient risk factor or is unprovoked[14,25].

In patients with a high clinical suspicion of acute PE, the guideline suggests treatment with parenteral anticoagulants rather than no treatment while awaiting the results of diagnostic tests. In patients with acute PE treated with LMWH, once-over twice-daily administration is suggested[25]. Patients with PE may have different pharmacokinetic responses to UFH, with a requirement for larger doses than those used in patients with DVT[27].

In patients with acute PE associated with hypotension (e.g., systolic blood pressure<90 mm Hg), who do not have a high bleeding risk, the guideline suggests systemically administered thrombolytic therapy over no such therapy because the patients are at an increased risk of death[25]. Systemic thrombolytic therapy is most commonly used, typically as 100 mg of tissue plasminogen activator given as a two-hour infusion[2,25].

Active removal of the thrombus is only considered for the roughly 5% of patients with PE who have hypotension, usually with other features of shock. This invasive procedure may be preferred if there is a high risk of bleeding, a poor response to systemic thrombolysis, or concern that the patient will die before systemic thrombolytic therapy has a chance to take effect[2,12,25,28].

## New Anticoagulants

The standard therapy in patients with PE has been the administration of heparin, overlapped and followed by VKAs[25,29]. This regimen is effective but complex because dose adjustment is necessary with UFH and VKAs have multiple food and drug interactions and a narrow therapeutic range[30]. Recently developed new oral anticoagulants (NOACs) that are directed against factor Xa or thrombin overcome some limitations of standard therapy, including the need for injection and for dose adjustments on the basis of regular monitoring[25,31,32].

Current data suggest that rivaroxaban, an oral direct inhibitor of factor Xa, is effective and safe for the prevention of VTE after major orthopedic surgery, for the prevention of stroke in patients with atrial fibrillation, and in the treatment of acute coronary syndromes[33-35]. In the studies involving patients with PE where NOACs only were used to replace VKAs, LMWH was typically used as initial therapy[36,37]. The EINSTEIN PE, which was a randomized, open-label, event-driven, non-inferiority phase III study, evaluated the treatment using rivaroxaban as the only anticoagulant for PE (with or without symptomatic DVT), replacing both heparin and VKAs[29]. This single-drug approach, starting with an increased dose (15 mg twice

daily for 3 weeks) followed by 20 mg once daily, appeared to be successful in treating PE with rivaroxaban compared with enoxaparin/VKA[29]. Rivaroxaban was administered with the same dose regimen in all patients without laboratory monitoring. Rates of recurrent VTE were similar in the two study groups regardless of age, sex, presence or absence of obesity, level of renal function, or extent of pulmonary embolism. There was actually a statistically significant reduction of major bleeding—but not of clinically relevant non-major bleeding[29]. Because bleeding is a major problem with anticoagulant therapy, these results seem to provide a favorable safety profile for rivaroxaban[27,29].

Another NOAC, dabigatran, is as effective as conventional anticoagulant therapy, does not require laboratory monitoring, and is associated with a lower risk of intracranial bleeding but a higher risk of gastrointestinal bleeding. Dabigatran is preceded by heparin therapy[37]. Both dabigatran and rivaroxaban are contraindicated if there is severe renal impairment and caution is needed if used with some drugs that are strong inducers or inhibitors of the efflux transporter P-glycoprotein. Dabigatran has been investigated in clinical trials in patients with VTE and has been shown to be non-inferior to warfarin in the prevention of recurrent VTE or related death in patients with acute symptomatic VTE[37,38]. Extended prophylaxis with dabigatran was associated with a 92% relative risk reduction for recurrent VTE compared with placebo in patients with VTE who had already received 6–18 months of anticoagulant therapy; however, higher rates of clinically relevant non-major bleeding were observed[38], which was also the case for rivaroxaban[29].

## How Often to Monitor International Normalized Ratio (INR) in Patients with Warfarin

Anticoagulant treatment with VKAs requires frequent PT monitoring and dose adjustment[30,39]. Most patients would prefer less frequent visits to the laboratory. The ACCP guideline recommends a maximum interval of 4 weeks[40]. A 1998 British guideline suggests PT monitoring up to every 12 weeks for very stable patients[39,41], but the evidence supporting a longer interval is limited. The analysis from Canadian center, where about one third of patients at this clinic has stable PT results without a change of maintenance VKA dose for at least 6 months, showed the safety and feasibility of 12 weeks interval compared with 4 weeks interval if they continue to have supportive contact with thrombosis clinic staff every 4 weeks[39]. Before prolonged intervals for testing and dose assessment can be recommended for practice, a phase III trial comparing INR testing and contact every 4 weeks with every 12 weeks would be necessary[39].

## Recurrence of VTE

The risk of recurrent VTE is high, with about one third of patients developing a recurrent event within 8 years[42]. In patients with a recurrent VTE requiring readmission, 50% of these events occur in the first 3 months after their initial DVT or PE[43,44]. In patients with symptomatic PE, rivaroxaban provided results consistent with those of other trials in which rates of recurrence of VTE in the standard-therapy group were 1.6% to 2.7% and the rates of major bleeding were 1.4% to 2.4%[29,45].

There are some studies on the prediction of recurrence of VTE. The PROLONG study demonstrated that in patients with at least 3 months of anticoagulation, if the qualitative D-dimer test was negative at 1 month after withholding warfarin, the annualized risk of recurrence was 6.2% compared with 15.0% if the D-dimer test was positive[46]. In a meta-analysis, the annual risk of recurrent VTE for patients with a negative, 1-month D-dimer was 3.5%[47]. The quantitative D-dimer testing was included in the Vienna prediction model with sex (higher risk for men) and the location of thrombosis (i.e., distal, proximal DVT, or PE with increasing risk)[48]. Recently, an international group published the simpler "DASH" rule, based on individual data from seven studies and including 1-month D-dimer, age, sex, and hormonal therapy[49,50].

## Optimal Duration of Anticoagulants

Currently, most patients are not treated indefinitely after first VTE episode although the risk of recurrence without anticoagulation therapy exceeds the risk of major bleeding with anticoagulation[50]. If PE has been effectively treated, there is the option to continue anticoagulants indefinitely to prevent recurrence of VTE. Extended therapy reduces the risk of recurrent VTE by over 90%, but increases the risk of bleeding two- to three-fold[25]. Annualized risk of major bleeding on extended treatment with NOACs, usually given after about 6 months of initial therapy, was 1.0% with rivaroxaban in EINSTEIN Extension[51], 0.7% with dabigatran in the RE-MEDY trial[38], and 0.6% with dabigatran in RE-SONATE[38]. Therefore the decision to treat indefinitely depends on balancing the increased risk of recurrence with stopping therapy against the increased risk of bleeding with continued therapy[25].

In ACCP 9th guideline, treatment for 3 months over shorter periods is recommended for proximal DVT or PE. For a first proximal DVT or PE provoked by surgery or by a nonsurgical transient risk factor such as estrogen therapy, 3 months of therapy is recommended[25,52]. After 3 months of treatment, patients with unprovoked PE should be evaluated for the risk-benefit ratio of extended therapy. In patients with a first VTE that is an unprovoked PE and who have a low or moderate bleeding risk, extended anticoagulant therapy over 3 months of therapy is suggested. Most patients with active cancer or

a second unprovoked VTE should receive extended therapy due to a high risk of recurrence[25].

## Vena Cava Filter

In patients with acute PE who are treated with anticoagulants, the ACCP 9th guideline recommends against the use of an IVC filter. In patients with acute PE and contraindication to anticoagulation, the use of an IVC filter is recommended to prevent emboli from reaching the lungs[12,25,53].

Removable filters can be used in patients with short term contraindications to anticoagulation, but only about 25% are removed and the long term safety of those that remain is uncertain[25].

## Isolated Subsegmental PE

Isolated subsegmental abnormalities reported in 10–20% of CT pulmonary angiograms, may be due to PE with symptoms or incidental findings, or may be false positive findings[2,54]. It might be challenging for clinician to decide to treat or not[2,55]. At a Canadian clinic patients with isolated subsegmental abnormalities are treated if there is clear evidence for PE (clear, usually multiple, defects on CT pulmonary angiography) with low risk of bleeding, whereas other patients are just monitored with serial ultrasound leg scans[2].

## Incidental PE

Incidental PE can be detected on a CT scan done for another reason and is asymptomatic[2,25]. The decision whether to treat or not, will depend on the evidence that PE is present (additional testing, such as CT pulmonary angiography), concomitant risk factors (presence of a hypercoagulable state such as cancer) and the patient's risk of bleeding[2].

## Cancer and PE

Most patients with active cancer-associated VTE should receive extended therapy because of a high risk of recurrence[25]. LMWH can be continued long term, which is generally preferred in patients with cancer-associated PE because of superior efficacy of LMWH, difficulty in controlling VKAs, and greater compatibility of LMWH with chemotherapy and the need for invasive procedures[25,56]. In the CLOT study, patient with cancer-associated VTE had a risk of major bleeding that was at least double that of patient without cancer[57,58].

## Pregnancy

In pregnant women with PE, treatment with NOACs (dabigatran or rivaroxaban) is not recommended because of a lack of clinical data. Current guidelines recommend LMWH as the preferred option in pregnant patients with PE[27,59].

## Insurance in Korea

In Korea, insurance plans cover the usage of rivaroxaban for the treatment of DVT (with or without PE) since early 2013 and for PE alone as of July 2013.

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