REVIEW

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Respiratory Review of 2014: Pulmonary Thromboembolism

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Venous thromboembolism (VTE), which includes pulmonary embolism and deep vein thrombosis, is an important cause of morbidity and mortality. The aim of this review is to summarize the findings from clinically important publications over the last year in the area of VTE. In this review, we discuss 11 randomized controlled trials published from March 2013 to April 2014. The COAG and the EU-PACT trials indicate that pharmacogenetic testing has either no usefulness in the initial dosing of vitamin K antagonists or marginal usefulness in the Caucasian population. Recent clinical trials with novel oral anticoagulants (NOACs) have demonstrated that the efficacy and safety of rivaroxaban, apixaban, edoxaban, and dabigatran are not inferior to those of conventional anticoagulants for the treatment of VTE. The PEITHO and ULTIMA trials suggested that rescue thrombolysis or catheter-directed thrombolysis may maximize the clinical benefits and minimize the bleeding risk. Lastly, riociguat has a proven efficacy in treating chronic thromboembolic pulmonary hypertension. In the future, NOACs, riociguat, and catheter-directed thrombolysis have the potential to revolutionize the management of patients with VTE.

Keywords: Venous Thromboembolism; Pulmonary Embolism; Pharmacogenetics; Anticoagulants; Thrombolytic Therapy

Introduction

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), is an important cause of morbidity and mortality in Western countries[1,2]. The incidence of VTE is about 1 per 1,000 subjects per year, with an incidence of PE approximately half that of DVT[3]. A recent national population-based epidemiological study reported a lower incidence of VTE in the Korean population (13.8 per 100,000 persons in 2008). However, it also demonstrated a yearly increasing incidence of VTE in Korea, and it is expected that the burden of VTE will increase with an increasing elderly population in Korea[4]. Preventing and managing VTE has progressed significantly over the past decade. The aim of this review is to summarize the findings from clinically important publications over the last year in the field of VTE. In this review, we discuss 11 randomized controlled trials published from March 2013 to April 2014. The discussion focuses on four topics: pharmacogenetics for warfarin dosing, novel oral anticoagulant (NOAC), thrombolysis in sub-massive PE, and new drugs for chronic thromboembolic pulmonary hypertension (CTEPH).

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Pharmacogenetic Study for Warfarin Dosing

1. The COAG trial: pharmacogenetic vs. a clinical algorithm for warfarin dosing[5]

Warfarin is used to prevent and treat thromboembolic diseases. There has been significant pharmacogenetic interest in the warfarin therapy to improve patients care. Two genes, *CYP2C9 and VKORC1* account for about 40% of the inter-individual variability in warfarin dose requirements[6]. The potential benefit of pharmacogenetic-guided warfarin dosing has not been investigated in randomized controlled trials. The COAG trial was a multicenter, double-blind, randomized trial that compared two approaches to guide initiation of warfarin therapy: initiating warfarin therapy based on algorithms using clinical information plus an individual's genotype using genes known to influence the warfarin response (genotype-guided dosing) vs. only clinical information (clinical-guided dosing). A total of 1,015 patients initiating warfarin therapy were randomly assigned to receive warfarin dosing during their first 5 days of therapy based on a dosing algorithm using both clinical variables and genotype information for *CYP2C9*2*, *CYP2C9*3*, and *VKORC1* or clinical data alone. None of the patients or clinicians was aware of the warfarin dose during the first 4 weeks of therapy. The primary endpoint was the percentage of time that the international normalized ratio (INR) was within the therapeutic range. There was no significant difference in the mean percentage of time in the therapeutic range (TTR) at 4 weeks between the genotype-guided group and the clinically guided group. However, a significant interaction was observed between race and dosing strategy. Among black patients, the mean percentage of TTR was less in the genotype-guided group than that in the clinically guided group, while there were no differences between groups among non-black patients. In conclusion, genotype-guided dosing of warfarin did not improve anticoagulation control in the COAG trial. These findings highlight the importance of developing and evaluating pharmacogenetic testing in patients from diverse racial and ethnic backgrounds.

2. The EU-PACT trial: randomized trial of genotype-guided dosing of warfarin[7]

The EU-PACT was a single-blind, multicenter, randomized controlled trial that enrolled 455 patients with atrial fibrillation or VTE receiving warfarin for the first time. Genotyping for *CYP2C9*2*, *CYP2C9*3*, and *VKORC1* (–1639G→A) was performed with a point-of-care test. Warfarin doses for patients assigned to the genotype-guided group were prescribed according to pharmacogenetic-based algorithms for the first 5 days. Patients in the control (standard dosing) group received a 3-day loading-dose regimen. After the initiation period, treatment of all patients was managed according to routine clinical practice. The primary outcome measure was the percentage of TTR of 2.0 to 3.0 during the first 12 weeks after warfarin was initiated. A total of 455 patients were recruited, with 227 randomly assigned to the genotype-guided group and 228 assigned to the control group. The mean percentage of TTR was 67.4% in the genotype-guided group compared with 60.3% in the control group (adjusted difference, 7.0 percentage points; 95% confidence interval [CI], 3.3–10.6; p<0.001). Significantly fewer incidences of excessive anticoagulation (INR≥4.0) were observed in the genotype-guided group. The median time to reach a therapeutic INR was 21 days in the genotype-guided group compared with 29 days in the control group (p<0.001). In conclusion, pharmacogenetic-based dosing was associated with a higher percentage of TTR than was standard dosing during the initiation of warfarin therapy.

NOAC Trials on VTE

1. The MAGELLAN trial: rivaroxaban for thromboprophylaxis in acutely ill patients[8]

Rivaroxaban is an oral direct factor Xa inhibitor that has advantages over traditional VTE therapies, including minimal drug and food interactions and no requirement for routine coagulation monitoring. It is currently approved for initial and long-term treatment in patients with acute DVT or PE[9,10], and also for preventing VTE in adult patients undergoing elective hip or knee replacement surgery[11,12]. The MAGELLAN trial was a randomized double-blinded trial that compared rivaroxaban with enoxaparin for preventing VTE in hospitalized patients with acute medical illness. The study population was aged ≥40 years and had been hospitalized with an acute medical illness and reduced mobility for <72 hours prior to randomization. A total of 8,101 patients were randomly assigned to receive oral rivaroxaban, 10 mg once daily, for 35 days or the standard dose of subcutaneous enoxaparin, 40 mg once daily, for 10 days and oral placebo for 35 days. All patients underwent bilateral ultrasonography to detect asymptomatic DVT at days 10 and 35. The primary composite efficacy outcomes included asymptomatic proximal DVT or symptomatic VTE up to day 10 and 35. The incidence of VTE at 10 days was not significantly different between the rivaroxaban group and the enoxaparin group (2.7% in each group). In the second phase of the trial (from day 10 to 35), the incidence of VTE in the rivaroxaban group was significantly lower than that in the placebo group (4.4% vs 5.7%, p=0.02). The primary safety outcome was the composite of clinically relevant major or non-major bleeding. A principal safety outcome event occurred in 2.8% of patients in the rivaroxaban group, in 1.2% of patients in the enoxaparin group on day 10 (p<0.001), and in 4.1% of patients in the rivaroxaban group and 1.7% of patients in the placebo groups on day 35

(p<0.001). A composite of the primary efficacy outcome and primary safety outcome was analyzed to determine the net clinical benefit or harm. Both outcomes had occurred on day 10 in 6.6% of the rivaroxaban group and 4.6% of the enoxaparin group (relative risk [RR] with rivaroxaban, 1.44; p<0.001). Both outcomes occurred on day 35 in 9.4% of the rivaroxaban group and 7.8% in the enoxaparin followed by the placebo group (p=0.02). In conclusion, rivaroxaban was not inferior to enoxaparin for thromboprophylaxis in acutely ill medical patients. However, rivaroxaban was associated with an increased risk of clinically relevant bleeding compared with enoxaparin.

2. The AMPLIFY-EXT trial: apixaban for extended treatment of VTE[13]

Apixaban is an oral factor Xa inhibitor with a rapid onset of action that is administered in fixed doses without the need for laboratory monitoring. Apixaban is effective for the prevention of VTE after major orthopedic surgery[14]. The AMPLIFY Extension study was a double-blind trial in which 2,486 patients with VTE were randomized to receive two different doses of apixaban (2.5 mg or 5 mg twice daily) or placebo after 6–12 months of anticoagulation treatment. Patients who completed treatment with apixaban or enoxaparin and warfarin as participants in the AMPLIFY trial could be included in this study; patients were eligible for inclusion in the AMPLIFY Extension study in case there was a clinical uncertainty regarding continued anticoagulation therapy. The study drugs were administered for 12 months. The rates of symptomatic recurrent VTE or death from VTE were 8.8 % in the placebo group, 1.7% in the 2.5 mg apixaban group, and 1.7% in the 5 mg apixaban group. The rates of major bleeding and clinically relevant non-major bleeding were 0.5% and 2.3% in the placebo group, 0.2% and 3.0% in the 2.5 mg apixaban group, and 0.1% and 4.2% in the 5 mg apixaban group. These results show that the 2.5 mg and 5 mg doses of apixaban are effective for reducing the rate of recurrent VTE without increasing the rate of bleeding compared to placebo. These results could provide a rationale for continuing anticoagulant therapy for an additional 12 months in patients with VTE for whom there is an uncertainty about the benefits and risks of continued anticoagulant therapy.

3. The AMPLIFY trial: oral apixaban for treating acute VTE[15]

In the AMPLIFY trial, 10 mg apixaban twice daily for 7 days and 5 mg followed by apixaban twice daily for 6 months was compared to conventional therapy of enoxaparin and warfarin in patients with acute VTE. The primary efficacy outcome was recurrent symptomatic VTE or death caused by VTE. The principal safety outcomes were major and clinically relevant non-major bleeding. The primary efficacy outcome occurred in 2.3% of patients in the apixaban group, and in 2.7% of patients in the enoxaparin-warfarin group (p>0.05). Major bleeding occurred in 0.6% of patients who received apixaban and in 1.8% of those who received enoxaparin and warfarin (p<0.001). The composite outcome of major bleeding and clinically relevant non-major bleeding occurred in 4.3% of the patients in the apixaban group, compared with 9.7% of those in the enoxaparin-warfarin group (p<0.001). Thus, a fixed dose of apixaban was not inferior to conventional therapy for treating acute VTE with a significantly decreased bleeding risk.

4. The RE-MEDY and the RE-SONATE trials: extended use of dabigatran, warfarin, or placebo in patients with VTE[16]

Dabigatran, a direct thrombin inhibitor, was not inferior to warfarin for the initial treatment of VTE (6 months) with a lower rate of clinically relevant non-major bleeding[17]. Two complementary trials were conducted to evaluate the efficacy and safety of dabigatran for extended duration of treatment in patients VTE. In the RE-MEDY trial, dabigatran was compared with warfarin; in the RE-SONATE trial, dabigatran was compared with placebo. A total of 2,866 patients who completed 3–6 months of anticoagulant therapy for their first VTE event were randomized to receive 150 mg dabigatran twice daily or warfarin in the RE-MEDY trial. The study design was initially planned for 18 months of treatment and then amended to increase the sample and extend the planned treatment period to 36 months. Dabigatran was not inferior to standard extended treatment with vitamin K antagonists (VKAs) for preventing recurrent symptomatic objectively confirmed VTE and VTE-related deaths (event rate 1.8% with dabigatran vs. 1.3% with warfarin; hazard ratio [HR], 1.47; 95% CI, 0.80–2.68). The rate of major bleeding complications was lower with dabigatran than that with warfarin (0.9% vs. 1.8%; HR, 0.52; 95% CI, 0.27–1.02). A trend for a higher rate of acute coronary syndrome with dabigatran with respect to warfarin was observed in this study. In the RE-SONATE study, patients treated for 6–18 months for a first VTE were randomized to receive 150 mg dabigatran twice daily or placebo for an additional 6 months. The study included 1,353 patients. A 92% RR reduction for symptomatic recurrent VTE was shown in favor of dabigatran (0.4% vs. 5.6% in the dabigatran and placebo group, respectively; HR, 0.08; 95% CI, 0.02–0.26). A 0.3% major bleeding rate was observed in the dabigatran group vs. 0% in the placebo group; clinically relevant non-major bleeding occurred in 5.3% of dabigatran patients and in 1.8% of placebo patients (HR, 2.92; 95% CI, 1.52–5.60). The rate of cardiovascular events was low in both groups. Whether dabigatran increased the risk of myocardial infarction was unclear. In conclusion, extended duration of treatment with dabigatran was not inferior to warfarin, but superior to placebo for preventing recurrent VTE. Dabigatran had a lower risk of bleeding than warfarin, but had a significantly higher risk of bleeding than placebo.

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5. The Hokusai-VTE trial: edoxaban vs. warfarin for treating symptomatic VTE[18]

Edoxaban is an oral, once-daily, direct factor Xa inhibitor. Hokusai-VTE was a randomized, double-blind, phase III study comparing 60 mg edoxaban qd (30 mg qd in patients with creatinine clearance of 30–50 mL/min, body weight≤60 kg) with warfarin for 3–12 months in patients with acute symptomatic DVT or PE. As in the dabigatran studies, Hokusai-VTE employed an initial treatment with low molecular weight heparin, for a median duration of 7 days, and patients treated with the study drug for 3–12 months. The primary efficacy outcome was recurrent symptomatic VTE. The principal safety outcome was clinically relevant bleeding. A total of 8.240 patients were randomized (4,118 to edoxaban and 4,122 to warfarin). A total of 4,921 patients had DVT and 3,319 patients had PE. Nearly 35% of patients had sub-massive PE. The time in the therapeutic range for warfarin was 63.5%. Edoxaban was not inferior to warfarin for reducing recurrent symptomatic VTE (3.2% vs. 3.5%; HR, 0.89; 95% CI, 0.70–1.13; p<0.001). The incidence of the composite of major or clinically relevant non-major bleeding was significantly lower with edoxaban compared with that of warfarin (8.5% vs. 10.3%; HR, 0.81; 95% CI, 0.71–0.94; p=0.004), although the incidence of major bleeding events was similar (1.4% vs. 1.6%; HR, 0.84; 95% CI, 0.59–1.21; p=0.35). In patients with sub-massive PE, edoxaban significantly reduced recurrent VTE (3.3% vs. 6.2%; HR, 0.52; 95% CI, 0.28–0.98). In conclusion, edoxaban was not inferior to warfarin in reducing recurrent VTE and reduced bleeding events in patients with VTE.

Thrombolysis for Acute PE

1. The TOPCAT trial: treatment of sub-massive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at three months (TOPCOAT): multicenter double-blind, placebo-controlled randomized trial[19]

The role of thrombolytic therapy in patients with sub-massive or intermediate risk PE is controversial. The TOPCOAT trial was a randomized controlled trial of tenecteplase plus low molecular weight heparin vs. placebo plus low molecular weight heparin in patients with sub-massive PE. Inclusion criteria were aged >17 years, PE diagnosed on computed tomographic angiography, and normal arterial systolic pressure with evidence of RV strain, manifested on echocardiography or by elevated cardiac biomarkers. All patients received therapeutic dose low-molecular-weight heparin followed by randomization to either a single weight-based bolus of tenecteplase or placebo. The primary composite efficacy outcomes included 1) death, circulatory shock, intubation or major bleeding within 5 days or 2) recurrent PE, poor functional capacity and health related quality of life at 90 days. 643 patients were screened, and 83 patients were randomized; 40 to tenecteplase and 43 to placebo. The trial was terminated early due to administrative issues. At 5 days, 3 placebo-treated patients had an adverse outcome (1 death and 2 intubation and vasopressor support) and 1 tenecteplase-treated patient died from intracranial hemorrhage. At 90 days, adverse outcomes occurred in 37% patients treated with placebo and 15% of patients treated with tenecteplase (p=0.017). In conclusion, a single bolus of tenecteplase had a modestly increased probability of a good functional outcome but the sample size was too small to assess the risk of hemorrhage.

2. The ULTIMA trial: randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk PE[20]

The ULTIMA trial was the first multicenter open-label, randomized, controlled trial to investigate whether the ultrasound-assisted catheter-directed thrombolysis (USAT) more rapidly reverse right ventricular (RV) enlargement than standard anticoagulation treatment in patients with acute intermediate-risk PE. Acute symptomatic PE patients confirmed by contrast-enhanced computed tomography with embolus located in at least one main or proximal lower lobe pulmonary artery and echocardiographic RV to left ventricular dimension (RV/LV) ratio≥1.0 were included in the ULTIMA trial. A total of 59 patients were randomized to receive unfractionated heparin and an USAT regimen of 10–20 mg recombinant tissue plasminogen activator over 15 hours (n=30, USAT group) or unfractionated heparin alone (n=29, heparin group). The primary end point was the difference in the RV/LV ratio from baseline to 24 hours. Safety outcomes included death, hemodynamic decompensation, major and minor bleeding, recurrent VTE and serious adverse events up to 90 days. In the USAT group, there was statistically significant reduction in mean RV/LV ratio at 24 hours; in the heparin group, there was no significant reduction. The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30±0.20 in the USAT group and 0.03±0.16 (p<0.001) in the heparin group. At 90 days, there was no statistically differences in bleeding events (three minor bleeding events in the USAT group and one in the heparin group), and there was no recurrent VTE in both groups. In conclusion, a standardized USAT treatment was clinically superior to anticoagulation alone for relieving RV dysfunction, without an increase in bleeding complications in patients with intermediate-risk PE.

3. The PEITHO trial: fibrinolysis for patients with intermediate-risk PE[21]

The PEITHO trial is a prospective, multicenter, international, randomized, double blinded study to demonstrate the clinical

benefit of thrombolysis with tenecteplase over placebo in patients with intermediate-risk PE. Age 18 years or older patients with acute PE were included if they had evidence of RV dysfunction on echocardiography or computed tomography, as well as myocardial injury as indicated by a positive test for cardiac troponin I or troponin T. The primary efficacy outcome was all-cause death or hemodynamic collapse within 7 days after randomization. The main safety outcomes included ischemic or hemorrhagic stroke and other major bleeding within 7 days after randomization, and serious adverse events within 30 days. A total of 1,006 patients were enrolled and a total of 1,005 patients were included in the intention-to-treat analysis. The primary efficacy outcomes was significantly reduced with tenecteplase (2.6% vs. 5.6% in the placebo group; odds ratio, 0.44; p=0.02). The clinical benefit of tenecteplase was driven by a significant reduction in the rate of hemodynamic collapse (1.6% vs. 5.0%, p=0.002). There was no statistical difference in all-cause mortality (1.2% in the tenecteplase group and 1.8% in the placebo group, p=0.42). Thrombolysis with tenecteplase was associated with a higher risk of bleeding complications. Major extra-cranial bleeding events were increased in the tenecteplase group compared with those in the placebo group (6.3% vs. 1.5%, p<0.001). There was also significant increased stroke events in the tenecteplase group compared with those the placebo group (2.4% vs. 0.2%, p=0.003). In the PEITHO trial, thrombolytic therapy with tenecteplase significantly reduced hemodynamic decompensation but increased the risk of intracranial and other major bleeding.

Chronic Thromboembolic Pulmonary Hypertension

1. The CHEST-1 trial: riociguat for treating of CTEPH[22]

The treatment of choice for patients with CTEPH is surgical pulmonary endarterectomy (PEA), which is the only curative therapy. To date, there are no approved drugs for CTEPH in Korea; as a result, there is unmet medical need for patients with inoperable CTEPH or patients with persistent or recurrent pulmonary hypertension (PH) after PEA. Riociguat is a novel drug that is a stimulator of soluble guanylate cyclase. It increases the level of cyclic guanosine monophosphate and synergizes with nitric oxide, resulting in vasodilatory and antiproliferative effects. The CHEST-1 trial was a first phase 3, randomized, double-blind study to assess the efficacy and safety of oral riociguat in the treatment of patients with inoperable CTEPH or persisted or recurred PH after PEA. A total of 261 patients were randomized and treated with either riociguat or placebo for 16 weeks. The primary efficacy endpoint was the change of six-minute walking distance (6MWD) from baseline to the end of week 16. Secondary efficacy endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, World Health Organization (WHO) functional class, time to clinical worsening, Borg dyspnea score, quality-of-life variables, and safety. Patients treated with riociguat demonstrated a statistically significant improvement of 6MWD from baseline after 16 weeks compared to placebo (least-squares mean difference 46 m; p<0.001). Riociguat also showed statistically significant improvements in secondary endpoints including PVR, NT-proBNP and WHO functional class. Riociguat showed a good safety profile in patients with CTEPH. The most frequent adverse events with riociguat were headache, dizziness, peripheral edema, and gastrointestinal symptoms. In conclusion, riociguat significantly improved exercise capacity and other clinical outcomes in patients with CTEPH. The US Food and Drug Administration approved riociguat for the treatment of CTEPH based on the results of CHEST-1 trial.

Conclusion

The conventional VTE treatment for the majority of the patients for several decades included an initial course of parental rapid-onset anticoagulants, followed by a long-term use (3–12 months) of oral VKAs. The COAG and the EU-PACT trials indicated that pharmacogenetic testing has either no usefulness in the initial dosing of VKAs or marginal usefulness in the Caucasian population. Taken together, data from recent clinical trials with rivaroxaban, apixaban, edoxaban, and dabigatran have established that the efficacy and safety of NOACs is at least comparable to those of conventional anticoagulants for treating VTE; therefore, these agents are an acceptable treatment option. Controversy remains over the role of fibrinolysis among normotensive patients with an intermediate risk for PE, recent trial data suggest that careful monitoring and rescue fibrinolysis or catheter-directed thrombolysis may maximize the clinical benefits and minimize the bleeding risk. Riociguat has been firstly approved for treatment of CTEPH. In the future, NOACs, riociguat, and catheter-directed thrombolysis have the potential to revolutionize the management of patients with VTE.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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