VTE: Treatment, Prevention of Recurrence, Thrombolysis

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Venous thromboembolism (VTE) is a common problem, at a prevalence of 1 to 2 VTEs per 1000 patients, with an in-hospital fatality rate of up to 12%. Victor F. Tapson, MD, Cedars-Sinai Medical Center, Los Angeles, California, USA, discussed the 3 novel oral anticoagulants (NOACs) that have become available for the treatment of VTE over the past 5 years.

As of October 2014, the US Food and Drug Administration (FDA) has approved the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban for the treatment of acute deep vein thrombosis (DVT) and pulmonary embolism (PE). These agents—as well as edoxaban, a factor Xa inhibitor that is under consideration by the FDA as of November 2014—have similar pharmacologic characteristics, including some metabolism by cytochrome P450 family members and transport by P-glycoprotein.

All the NOACs have at least some protein binding in circulation; however, less protein binding occurs with dabigatran (35%) [Blech S et al. *Drug Metab Dispos.* 2008], with the implication that, unlike the other NOACs, it is dialyzable, which may be important if a bleed occurs. Dr Tapson also pointed out that renal clearance is a relevant patient characteristic to be aware of when using the NOACs. Apixaban has the lowest renal clearance, 25% [Raghavan N et al. *Drug Metab Dispos.* 2009], whereas dabigatran has the highest amount, ≤80% [Stangier J et al. *Br J Clin Pharmacol.* 2007]. Pivotal trials for the NOACs are listed in Table 1.

The rates of the primary end point of recurrent VTE—whether DVT or PE—were similar among the NOACs and were noninferior to warfarin. In general, the NOACs resulted in less severe bleeding when compared with that of warfarin in the pivotal trials, and rivaroxaban and apixaban achieved superiority over warfarin for incidence of major bleeding.

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Dr Tapson discussed NOAC drug-drug interactions, noting that clinicians should be aware that strong CYP3A4 inhibitors combined with P-glycoprotein inhibitors should be avoided. For example, carbamazepine, phenytoin, rifampin, and St John's wort should be avoided with rivaroxaban and apixaban, whereas concomitant P-glycoprotein inducers such as rifampin should be avoided with dabigatran. Furthermore, when used for the treatment of VTE, dabigatran and rivaroxaban should be avoided in patients with a creatinine clearance <30 mL/min, and apixaban should be used with caution.

Richard N. Channick, MD, Massachusetts General Hospital, Boston, Massachusetts, USA, discussed the prevention of recurrent VTE. Thirty percent of patients will experience VTE recurrence by 10 years, with the greatest risk occurring 6 to 12 months after acute VTE. Long-term anticoagulation is highly effective in preventing VTE recurrence but must be balanced with an increased risk of bleeding. In addition, there is a risk of VTE recurrence after discontinuation of anticoagulation, which is most likely in the first 2 to 3 months after discontinuation. Dr Channick outlined 3 phases of anticoagulation: the initial phase, which lasts for 5 to 7 days and is the period associated with the greatest risk of VTE recurrence; the long-term phase, which lasts from 7 days to 3 months and is the minimum recommended amount of time for anticoagulation; and the extended phase, which is >3 months.

Determining a patient's risk of recurrence is based on his or her characteristics, the presence of risk factors, and the nature of the original VTE. For example, if the initial VTE was PE, the patient is more likely to have a PE recurrence than a proximal DVT. Risk factors for VTE recurrence include age, PE as the index event, and elevated D-dimer. It is also important to consider a patient's risk of bleeding.

There are 3 types of patients, each with a different anticoagulation recommendation. In patients with a transient risk factor, anticoagulation can be discontinued after 3 months, whereas patients with an ongoing risk factor, such as cancer, should receive continued anticoagulation.

Table 1. Pivotal Trials for Novel Oral Anticoagulants

Agent	Trial	Design	Heparin Bridge	Journal
Dabigatran	RE-COVER	Double-blind	Yes	Schulman S et al. *N Engl J Med.* 2009
Rivaroxaban	EINSTEIN-DVT	Double-blind	No	EINSTEIN Investigators. *N Engl J Med.* 2010
Rivaroxaban	EINSTEIN-PE	Open-label with blinded end point	No	EINSTEIN-PE Investigators. *N Engl J Med.* 2012
Apixaban	AMPLIFY	Double-blind	No	Agnelli G et al. *N Engl J Med.* 2013
Edoxaban	Hokusai-VTE	Double-blind	Yes	Hokusai-VTE Investigators. *N Engl J Med.* 2013

In patients who experience an unprovoked VTE, anticoagulation should be continued for at least 3 months and then reconsidered on the basis of a risk-benefit analysis and the patient's preference.

In addition to the NOACs and warfarin, aspirin can be used to prevent VTE recurrence. In 2 randomized controlled trials, 100 mg/d of aspirin reduced the relative risk of experiencing VTE recurrence with a low rate of bleeding [Becattini C et al. *N Engl J Med.* 2012; Brighton TA et al. *N Engl J Med.* 2012].

Susan Murin, MD, MSc, University of California, Davis, Sacramento, California, USA, discussed thrombolytic therapy for the treatment of acute PE. Currently, there are 3 agents approved by the FDA for thrombolysis in PE: streptokinase, urokinase, and tissue plasminogen activator (alteplase). Although thrombolysis dissolves the clot, it is associated with an increased risk of bleeding. In addition, it is unknown whether the short-term improvement in hemodynamics and perfusion in patients treated with thrombolysis translates into long-term meaningful outcomes.

Ultrasound-assisted catheter-directed thrombolysis plus heparin resulted in greater improvements when compared with heparin alone in 1 study [Kucher N et al. *Circulation.* 2014]. In addition, the rate of bleeding was comparable to that observed in trials that evaluated systemic thrombolysis.

Dr Murin suggested that thrombolysis be routinely used in patients with PE and shock who do not have contraindications. In addition, thrombolysis should be considered but not routinely administered in patients with intermediate risk for PE. Finally, systemic thrombolysis is preferred over catheter-directed thrombolysis in patients who have an average risk of bleeding.