Patients (n=5400; mean age, 57 years; 58% men) were enrolled at 358 centers in 28 countries and assigned to receive either apixaban (n=2691) or conventional therapy (n=2704). Approximately 65% of patients entered the study with DVT, 25% with PE, and ~9% with DVT plus PE. VTE was unprovoked in 90% of patients. Most (75%) patients had a femoral or more proximal DVT, while 38% had extensive PE that included ≥2 lobes with ≥50% of the vasculature for each lobe affected.

After 6 months, 57 (2.3%) of the patients receiving apixaban experienced a first recurrent VTE or VTE-related death compared with 71 (2.7%) receiving conventional therapy. Apixaban was noninferior to conventional treatment (relative risk [RR], 0.84; 95% CI, 0.60 to 1.18; p<0.0001 for noninferiority; Table 1). Similar results were seen with the secondary outcomes.

Table 1. Efficacy Outcomes

	Apixaban (n=2609)	Enoxaparin/ Warfarin (n=2635)	Relative Risk (95% CI)	p Value
First recurrent VTE or VTE-related death, n (%)	59 (2.3)	71 (2.7)	0.84 (0.60 to 1.18)	<0.0001 for noninferiority
Index event: DVT	38/1698 (2.2)	47/1736 (2.7)	0.83 (0.54 to 1.26)	
Index event: PE±DVT	21/900 (2.3)	23/886 (2.6)	0.90 (0.50 to 1.61)	
VTE or CV-related death, n (%)	61 (2.3)	77 (2.9)	0.80 (0.57 to 1.11)	
VTE or all-cause death, n (%)	84 (3.2)	104 (4.0)	0.82 (0.61 to 1.08)	

Days to first recurrent VTE or VTE-related death, the majority of which occurred in the first 30 days, were similar in the two treatment groups. The percentage of time in therapeutic range was 60.9% for warfarin-treated patients.

In the apixaban group, 15 (0.6%) patients had major bleeding versus 49 (1.8%) in the conventionally treated group (RR, 0.31; 95% CI, 0.17 to 0.55; p<0.0001 superiority for apixaban). Clinically relevant nonmajor bleeding and major or clinically relevant nonmajor bleeding occurred in 3.9% and 4.3% of patients in the apixaban group and 8.0% and 9.7% of patients in the conventional group, respectively.

Apixaban administered in a simple, fixed-dose regimen, may be an option for the extended treatment of VTE. It is noninferior to conventional therapy for preventing recurrent VTE, with similar efficacy in patients with DVT and PE, and clinically important and statistically significant reduction in major bleeding of 69%.

This study was simultaneously published [Agnelli G et al. *N Engl J Med* 2013].

In Search of the Holy Grail of Anticoagulant Therapy

Written by **Wayne Kuznar**

The trade-off between antithrombotic effect and bleeding hinders the efficacy of current anticoagulant therapy. An antibody in development has demonstrated dissociation of the antithrombotic effect from the bleeding effect in preclinical studies, showing promise as a revolutionary drug for the treatment of thrombosis, said Trevor Baglin, MB, ChB, PhD, Addenbrookes Hospital, Cambridge, United Kingdom.

He described a naturally occurring antibody discovered in a 54-year-old woman with a chronic subdural hematoma due to a head injury. The patient had a degree of anticoagulation consistent with hemophilia. *In vitro* coagulation assays showed a prothrombin time of 50 seconds, an activated partial thromboplastin time of 189 seconds, and a thrombin time >60 seconds, which normally would cause a life-threatening bleeding disorder. Yet, the patient recovered fully (no neurologic deficit) with conservative treatment without further intervention. Her only other relevant history was having undergone knee surgery 5 months prior with no bleeding episode; a preoperative clotting screen was not performed at that time.

The patient was found to have an acquired inhibitor of coagulation in the form of a monoclonal paraprotein immunoglobulin (Ig)A, present in her natural serum at a level of >5 g/L^{-1}. The antibody was purified by Jacalin agarose and when added back to plasma, was a potent inhibitor of thrombin, binding with a Kd of 1 nM, with a fast on-rate and slow off-rate. Exosite 1 binding was suggested by inhibition of fibrinogen cleavage but with retained cleavage of a small reporter molecule (a fluororphore). Competitive binding with fluorescently labeled hirugen confirmed exosite 1 as the binding site on thrombin. A Fab fragment was prepared from the antibody and cocrystallized with human PPACK-thrombin, and a 1.9Å structure was solved showing an interaction between the antibody and exosite 1 of thrombin, the main point of contact being CDRH3 of the antibody.

The purified antibody was tested in two animal models of arterial thrombosis. At a maximum concentration of 4 nM, which completely abolished thrombosis, tail bleeding times were not prolonged. At 40nM and higher concentrations of the antibody, fibrin deposition was reduced both early and late. In a murine carotid artery occlusion-model, with a 5% ferric chloride injury, the antibody prevented arterial occlusion and maintained blood flow in 4 of 7 animals. At the maximum concentration

studied (400 nM), blood loss from a tail clip was not increased compared with saline controls.

By comparison, at 5% ferric chloride, a dose of heparin (200 U/kg) that causes bleeding in all animals in this thrombosis/bleeding model has no effect on arterial thrombosis, said Dr. Baglin. At 1000 U/kg, heparin reduces occlusion but universally causes fatal bleeding.

He concluded that an antibody that appears to prevent thrombosis without causing bleeding has been identified. A therapeutic derivative of this IgA may potentially permit unlimited dose escalation of antithrombotic therapy without increasing bleeding, given the dissociation of the antithrombotic effect from the bleeding effect.

Use of Dalteparin Beyond 6 Months in Cancer Patients With VTE Is Feasible

Written by **Maria Vinall**

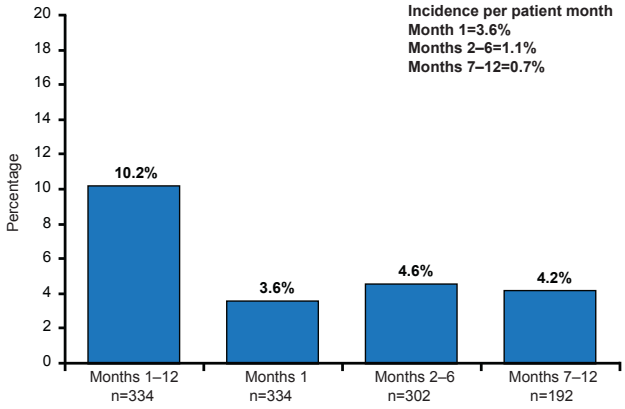
Although the guidelines for treating venous thromboembolism (VTE) in cancer patients recommend anticoagulation with low-molecular-weight heparin for at least 3 to 6 months, or for the duration of the malignancy, uncertainty exists concerning whether to extend anticoagulation longer to prevent recurrence of VTE. In a study presented by The Lord Ajay K. Kakkar, MD, University College London, London, United Kingdom, dalteparin sodium administered beyond 6 months was not associated with an increase in bleeding relative to the initial period of therapy.

The objective of the Evaluation of Dalteparin for Long-Term (One Year) Treatment of Blood Clots in Subjects With Cancer study [DALTECAN; NCT00942968] was to assess the consequences of extending anticoagulation with dalteparin beyond 6 months in cancer-associated VTE. This was a Phase 4 multicenter, single-arm, open-label study that enrolled men and women aged ≥18 years with histologically confirmed cancer and a new VTE (objectively confirmed deep vein thrombosis [DVT], proximal vein thrombosis, pulmonary embolism, or both). All patients received treatment with dalteparin 200 IU/kg daily subcutaneously for 1 month, followed by 150 IU/kg daily for up to 11 months. The study was conducted at 50 sites in the United States, Europe, and Canada.

The primary study endpoint was major bleeding events for Months 7 to 12 relative to Months 2 to 6 of dalteparin therapy. Secondary endpoints included rate of recurrent VTE, time to symptomatic recurrent VTE, rate of minor bleeding events, time to first major or any bleeding event, and safety and tolerability of extended treatment with dalteparin. Bleeding and recurrent VTE were centrally adjudicated.

Patients had a mean age of 64 years and about half were men. Most (78%) were Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1. Of the 334 patients who received drug treatment, 109 (32.2%) completed the 12-month study. Of the 229 patients who discontinued the study, 76 were due to death and 60 were due to an adverse event. The remaining discontinuations were due to withdrawal of consent (n=42) or "other" reasons (n=51). Most (92%) patients had solid tumors and the majority was stage III or IV. Therapy adherence was 96% across the entire cohort, with a median treatment duration of 211 days. The overall frequency of major bleeding was 10.2%, observed at a rate of 1.3% per patient-month.

Figure 1. The Incidence of Major Bleeding Events



The highest major bleeding rate was in the first month of dalteparin therapy at 3.6%, with the frequency declining to 1.1% during Months 2 to 6, and 0.7% over Months 7 to 12, with no statistically significant difference in rates between Months 2 to 6 and 7 to 12 (p=0.39). The incidence of all bleeding events was 13.2% in Month 1, 4.5% in Months 2 to 6, and 2.7% in Months 7 to 12, with a total 1 to 12 month incidence rate of 33.5%.

The incidence of new or recurrent VTE was 11.1% (37 patients), a rate of 1.4% per patient-month. The rate was highest for Month 1 at 5.7%, falling thereafter to 0.8% per month for Months 2 to 6 (incidence 3.4%) and 0.7% per month for Months 7 to 12 (incidence 4.1%). The investigators were unable to identify any predictive factors for the occurrence of VTE.