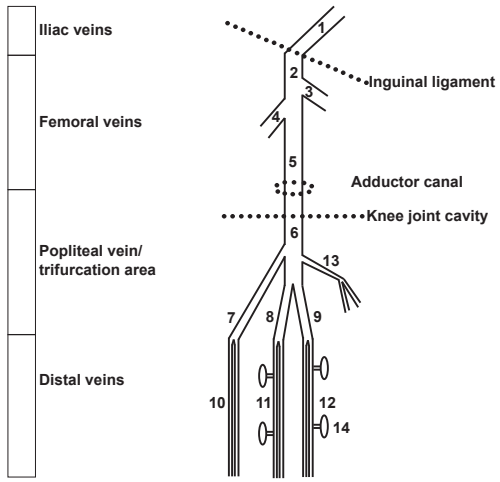
Figure 1. Diagram of the Distal (Calf) Vein



Schematic representation of leg veins: 1) External iliac vein; 2) Common femoral vein; 3) Greater saphenous vein; 4) Profound femoral vein; 5) (Superficial) femoral vein; 6) Popliteal vein; 7) Anterior tibial confluent segment 8) Posterior tibial confluent segment; 9) Peroneal confluent segment; 10) Anterior tibial veins; 11) Posterior tibial veins; 12) Peroneal veins; 13) Gastroenemius muscle veins (medial head); 14) Soleus muscle veins.

Reproduced from Palareti, G, Schellong S. Isolated distal deep vein thrombosis: what we know and what we are doing : Isolated distal DVT. *J Thromb Haemost* 2012;10(1)11-19. With permission from the International Society of Thrombosis and Haemostasis.

Table 2. Composite Outcomes with Individualized Components

	Conservative Management (n=35)	Therapeutic Anticoagulation (n=17)	ARR % (95%CI)	p Value
Composite outcome	4 (11.4)	0 (0)	11.4% (-1.5 to 26.7)	p=0.11
Popliteal Propagation	3 (8.6)	0 (0)	8.6% (-3.5 to 23.1)	ns
PE	1 (2.9)	0 (0)	2.9% (-7.5 to 15.0)	ns
VTE-related death	0 (0)	0 (0)		ns
Major bleeding	0 (0)	0 (0)		ns
Minor bleeding	3 (8.6%)	7 (20.0)	-11.4% (-29.7 to 7.1)	ns
Nuisance bleeding	9 (25.7)	9 (25.7)		ns
Investigated for suspected PE	4 (11.4)	0 (0)	11.4% (-1.5 to 26.7)	ns
Sudden adverse event rate	7 (20.0)	8 (22.9)	-2.9% (-18.1 to 23.7)	ns
Adverse event rate	17 (48.6)	9 (25.7)	22.9% (-1.7 to 44.8)	ns

PE=pulmonary embolism; VTE=venous thromboembolism.

Propagation to any site (as recorded by an increasing Marder score at any stage during 3-month follow-up) occurred in 11 (31.4%) control patients compared with 2 (5.7%) intervention patients (ARR 25.7%; 95% CI, 5.9 to 44.3; p=0.01; NNT, 4). There was an increased rate of resolution in the intervention group but it was not significant (p=0.3).

The results of this study indicate that further primary research regarding IDDVT is feasible within a modern healthcare framework. The point estimate for the ARR in serious thromboembolic complications with therapeutic anticoagulation is roughly 11%. Limitations of the study include the use of sonography instead of contrast venography, a relatively short endpoint, and being a single-center study. The results of this pilot study will be used to plan a more definitive multicenter trial.

Apixaban Is an Effective Replacement for Conventional Anticoagulation Therapy

Written by Maria Vinall

Apixaban, an oral factor Xa inhibitor, is noninferior to enoxaparin plus warfarin for the treatment of acute symptomatic proximal deep vein thrombosis (DVT) and pulmonary embolism (PE), and is associated with significantly less bleeding compared with conventional therapy. Administered in fixed doses, apixaban may simplify the treatment of acute venous thromboembolism (VTE). Giancarlo Agnelli, MD, University of Perugia, Perugia, Italy, presented the results of the Efficacy and Safety Study of Apixaban for the Treatment of Deep Vein Thrombosis or Pulmonary Embolism [AMPLIFY; NCT00643201].

The purpose of this 6-month, randomized, double-blind, noninferiority trial was to compare the efficacy and safety of apixaban (10 mg BID for 7 days, followed by 5 mg BID) with conventional anticoagulant therapy consisting of subcutaneous enoxaparin (1 mg/kg BID) followed by warfarin (target INR 2 to 3). The study enrolled adults with acute symptomatic proximal DVT or PE. The criteria for noninferiority required that the upper limit of the 95% CIs be below prespecified margins for both the relative risk (<1.8) and the absolute risk difference (<3.5%). The diagnosis at study entry, the extent of initial DVT or PE, and all suspected outcomes were adjudicated by an independent committee, whose members were unaware of study group assignments.

The primary efficacy outcome was symptomatic recurrent VTE or VTE–related death. Other outcomes included recurrent symptomatic VTE or cardiovascular-related death, and recurrent symptomatic VTE or all-cause death. The primary safety outcome was adjudicated major bleeding. The secondary safety outcome was the composite of major bleeding and clinically relevant nonmajor bleeding.

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