Anticoagulation for Isolated Distal Deep Vein Thrombosis May Reduce Serious Complications

Written by **Maria Vinall**

A feasibility study has provided new insight on the value of therapeutic anticoagulation for isolated distal deep vein thrombosis (IDDVT). This pilot study reported a nonsignificant trend toward reduction of serious complications, including the absence of major bleeding, with anticoagulation. Daniel Horner, MD, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, reported the results of the study.

Half of all lower limb deep vein thrombi are located in the distal (calf) veins (Figure 1) [Palareti G, Schellong S. *J Thromb Haemost* 2012].

There is currently little evidence defining the clinical importance of detecting and treating IDDVT. Contemporary international guidelines vary regarding diagnostic and therapeutic advice. One meta-analysis suggested that anticoagulation therapy for IDDVT may decrease the rate of subsequent pulmonary embolism and thrombus propagation, but findings were not robust [De Martino RR et al. *J Vasc Surg* 2012]. Thus, the risk and benefits of anticoagulation therapy remain poorly defined.

The Anticoagulation of Calf Thrombosis trial [ACT; ISRCTN75175695] aimed to compare therapeutic anticoagulation against conservative management for patients with acute symptomatic IDDVT.

The ACT study was a pragmatic, open-label, randomized controlled trial within a modern healthcare framework conducted to determine whether patients with IDDVT benefit from therapeutic anticoagulation. Principal feasibility outcomes included incidence of the index condition, recruitment rate and attrition (including loss to follow-up, protocol violation, and allocation crossover). A composite of thrombus propagation to the popliteal vein, symptomatic pulmonary embolism, death attributable to venous thromboembolic disease, or major bleeding was the primary clinical outcome. Propagation to any site, symptomatic progression, and minor or nuisance bleeding rates were secondary clinical outcomes.

Symptomatic IDDVT patients within a single ambulatory thrombosis center were included in the study. Participants were randomized to receive either phased therapeutic anticoagulation intervention (n=35) or conservative management (n=35). Both groups received Grade 2 compression stockings and analgesia. All patients underwent assessor-blinded, color-duplex sonographic imaging after 7 and 21 days, and follow-up at 3 months. Analysis was by intention-to-treat.

All predefined feasibility outcomes were achieved (Table 1).

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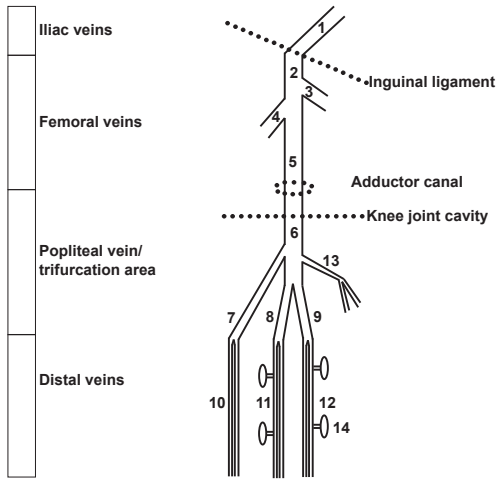
Table 1. Predefined Feasibility Criteria

Criterion	Aim	Result
Incidence of IDDVT within the ambulatory cohort	>5%	9.8%
Eligible patients agreeing to participate	>70%	88.6%
Completion of full study protocol	>50%	84.3%
Allocation crossover	<25%	21.4%

IDDVT=isolated distal deep vein thrombosis.

The primary clinical outcome occurred in 4 of the patients in the control group and no one in the intervention group (absolute risk reduction [ARR], 11.4%; Table 2). The number-needed-to-treat (NNT) was 9. There were no cases of major bleeding in either group. Minor bleeding occurred in 3 (8.6%) patients in the control and 7 (20.0%) in the intervention groups (p=0.31). Allocation crossover occurred in 15 (21.4%) patients.

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.