Conclusions: (1) The number of cycles has an impact on the depth of the vein wall damage. (2) One treatment cycle does not cause damage to all layers of the vein wall. (3) Three treatment cycles cause damage to all vein wall layers.

P-Selectin Inhibition Therapeutically Promotes Thrombus Resolution and Prevents Vein Wall Fibrosis Better than Enoxaparin and an Inhibitor to von Willebrand Factor

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Background: P-selectin (P-sel) and von Willebrand factor (VWF) promote venous thrombosis (VT). Aptamers are oligonucleotides targeting protein/protein interactions like P-sel, VWF, and their ligands. This study tested the therapeutic effects of aptamers against P-sel and VWF compared with a low molecular weight heparin, enoxaparin, on experimental VT.

Methods: Male juvenile baboons underwent experimental iliac VT. Occlusive thrombus was created and confirmed on day 0, and treatment initiated 2 days post-VT. Treatment groups included: controls with no treatment (n = 3); anti-P-sel aptamer ARC5692 (2 mg/kg intravenously [IV] + 1 mg/kg subcutaneously [SQ]), then 1 mg/kg SQ twice a day until euthanasia on day 21 (n = 3); anti-VWF Aptamer ARC15105 (250 μg/kg IV), then single doses of 250 μg/kg IV on days 6, 10, and 14 (n = 3); and enoxaparin 1.5 mg/kg SQ daily until day 21 post-VT. Coagulation tests, hematology, magnetic resonance venography, contrast venography, and ultrasonography were performed on days 0, 2, 6, 14, and 21. At 21 days, inferior vena cava and iliac veins were harvested for histology. Therapeutic levels of drugs were confirmed by high-performance liquid chromatography and Xa.

Results: P-sel inhibition (ARC5692) resulted in a significant improvement in percent vein reopening and vein valve competency with less vein wall fibrosis, as measured by percent collagen deposition obtained on trichrome analysis, compared to enoxaparin and anti-VWF aptamer. Additionally, P-sel inhibition resulted in no elevation of coagulation functions (Table).

Conclusions: P-sel inhibition therapeutically promotes thrombus resolution and prevents vein wall fibrosis better than enoxaparin and an inhibitor to VWF. P-sel inhibition exhibits an improved therapeutic benefit over the current standard of care and thus should undergo future clinical trials for the treatment of VT.

Table.

	Control	*P-sel inhibitor*	*Enoxaparin*	*VWF inhibitor*
MRV (% reopening [after total thrombosis])	13%	73% ↑	42%	0%
Vein value competence (after total thrombosis)	0%	33%	33%	0%
Fibrosis (% collangen deposition)	46%	39% ↓	54%	49%
aPTT, seconds (range 21-45)	40	43	56 ↑	41
Bleeding time, minutes (range 1-8)	5	4	10 ↑	20 ↑

aPTT, Activated partial thromboplastin time; *P-sel,* P-selectin; *VWF,* von Willebrand factor.
Arrows indicate significant increase or decrease ($P \leq .05$).

Regional and Systemic Prothrombotic Biomarkers in Varicose Vein Patients and Healthy Controls

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Background: The relationship between thrombosis and varicose veins is poorly understood. Varicose veins are seen in approximately 50% of patients with post-thrombotic syndrome and may be a risk factor for thrombosis. Furthermore, hemostatic markers are assessed usually from arm blood. Recirculating leg blood may be different in varicose veins. The aim of this study was to determine whether prothrombotic biomarkers varied between patients with varicose veins and healthy controls and whether standard venous samples from the arm differed from leg samples.

Methods: This was a prospective study on 24 patients (17 male; median age, 45 years [range, 25-91 years]) awaiting saphenous laser ablation and 24 healthy volunteers (17 male; median age, 42 years [range, 24-89 years]) without venous disease. The clinical CEAP distribution was: C_2, 6; C_3, 4; C_{4a}, 1; C_{4b}, 6; C_5, 5; C_6, 2; with a median Venous Clinical Severity Score and refluxing saphenous vein diameter of 6 mm (range, 4-10 mm) and 8.2 mm (range, 6-12 mm), respectively. Five mL of venous blood was taken from the antecubital fossa, with a concurrent sample from a varicose tributary (patients) or foot vein (volunteers). The following tests were performed: thrombin-antithrombin (TAT) ng/mL, anti-thrombin III (ATIII) % activity, microparticles (MP) nM, fibrinogen mg/dL, prothrombin fragments 1.2 (F1.2) pmol, P-selectin ng/mL, and dilute Russell's viper venom time (DRVVT) sec. The data were analyzed using the Wilcoxon test (same subject) and the Mann-Whitney test (different subjects).

Results: Significant differences (**) were observed between patients and controls as well as between arm and leg samples in all of the hemostatic markers, except fibrinogen (Table). As depicted in the Fig, TAT levels differed significantly from the control arm sample when compared against patients with varicose veins or leg samples. Evidence to support an increase in thrombotic activity in varicose vein patients is from statistically elevated TAT, ATIII, and F1.2. However, the relationship was inverse with MP and DRVVT. Evidence to support an increase in thrombotic activity in legs > arms is from statistically elevated TAT levels. However, the relationship was significantly inverse with ATIII and F1.2.

Conclusions: There is conflicting evidence for thrombosis risk assessment by elevated venous biomarkers in patients with varicose veins or leg samples. However, the differences observed between arm and leg samples require explanation. Venous leg sampling opens up a new anatomical site of investigation which may have future clinical value.

Table. *P* values of hemostatic markers comparing patients with controls and arms with legs

	Patient	*Control*	*Arm*	*Leg*
	Arm vs leg	*Arm vs leg*	*Patient vs control*	*Patient vs control*
TAT (ng/mL)	.415	.015**	.038**	.585
AT III (% activity)	.001**	.201	.003**	.007**
MP (nM)	.819	.116	.543	.020**
Fibrinogen (mg/dL)	.749	.128	.409	.173
F1.2 (pmol)	.587	.028 **	.386	.026**
P-selectin (ng/mL)	.044**	.007**	.108	.606
DRVVT (seconds)	.091	.097	.048**	.205

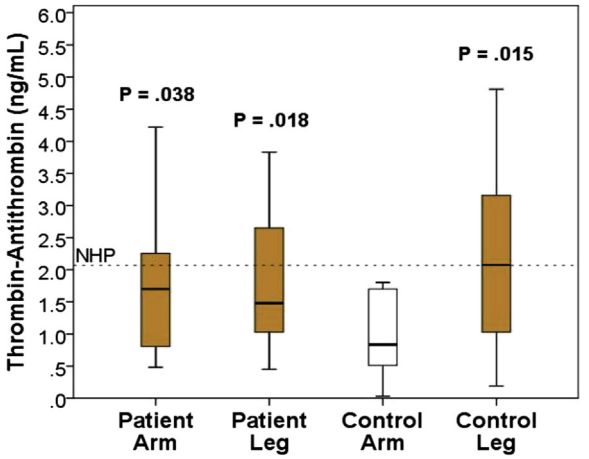

Fig. The thrombin-antithrombin (TAT) levels in the normal control subjects were significantly lower than the levels in varicose vein patients and in the control legs.