Management of Post Thrombotic Syndrome: What are the Current Options in Care?

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Disclosures

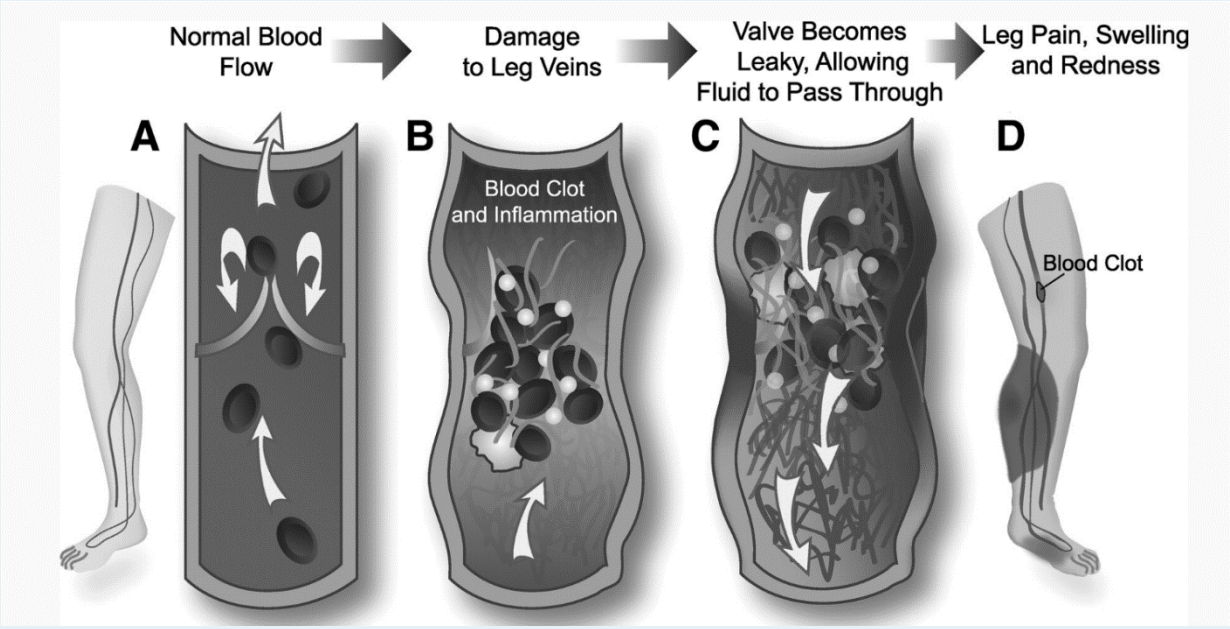
- I have the following financial relationships to report with ACCME-defined ineligible companies.

Name of Company	Nature of Relationship	Current Status
Inari	Consultant	Active
Mercator	Consultant	Active
Penumbra	Consultant	Active

- I will be discussing investigational uses of dexamethasone sodium phosphate, injection, and the use of experimental deep venous valves during this presentation.

Why treat DVT?

- Early return of vein patency
- Preserve valvular function to limit long term complication
- Prevent pulmonary embolism
- Limit Post-thrombotic syndrome



	Cumulative incidence		Survival rate
	Recurrent DVT	Post-thrombotic syndrome	
2 years	17%	25%	80%
5 years	24%	30%	74%
8 years	30%	30%	69%

Sara R. Vazquez Susan R. Kahn **Postthrombotic Syndrome**

Circulation 2 Mar 2010. 2010;121:e217–e219

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Prandoni 96, Prandoni 98; Prandoni 97

Heparin vs. Thrombolysis
Comparison of 13 studies

Outcome	Heparin	Thrombolysis
	N=254	N=337
Complete Lysis	4%	45%
Partial Lysis	14%	18%
No Change/Worse	82%	37%

Comerota A, Aldridge S. *Semin Vasc Surg.* 1992;5(2):76-81.

Sequelae of DVT

- Post-thrombotic syndrome may result in:
  - Chronic pain
  - Swelling
  - Skin ulceration secondary to post-phlebitic syndrome
- Chronic condition in 30-75% of DVT patients within 2 years
  - 90% unable to work due to leg symptoms 10 years after iliofemoral DVT
- Irreversible damage to veins & valves
  - **Impact on quality of life**

1. Geerts et al. Chest. 2004;126(suppl):338S-400S
2. Parikh et al JVIR 2008 19; 521-528
3. Kahn SR, Ginsberg JS. "Relationship Between Deep Venous Thrombosis and the Post thrombotic Syndrome". Arch Intern Med 2004; 164:17–26.

Post-Thrombotic Syndrome

- PTS develops in 29% to 74% of patients following DVT
- Affects 5% of US population
- 400,000 to 500,000 individuals have venous stasis ulcers
- Annual direct cost of PTS in the US of $200 million
- 2 million workdays lost annually in the US

Heit, *J Vasc Surg* 2001
Phillips, *J Amer Acad Derm* 1994

Greater thrombus removal gives lower PTS rate

Comerota et al. J Vasc Surg. 2012 Mar;55(3):768-73.

Journal of Vascular Surgery®

Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis

Anthony J. Comerota, MD,[a] Nina Grewal, MD,[a] Jorge Trabal Martinez, MD,[a] John Tahao Chen, PhD,[b] Robert DiSalle, MD,[a] Linda Andrews, RN,[a] Deb Sepanski, RT(R),[a] and Zakaria Assi, MD,[a] *Toledo and Bowling Green, Ohio*

Background: Iliofemoral deep vein thrombosis (DVT) is associated with severe postthrombotic morbidity when treated

correlation of clinical class of CEAP with residual thrombus ($R^2 = .74$; $P = .004$) and a direct linear correlation of Villalta score with residual thrombus ($R^2 = .61$; $P = .0014$).

Conclusion: In patients with iliofemoral DVT treated with catheter-based techniques of thrombus removal, postthrombotic morbidity is related to residual thrombus. When thrombus clearance was complete, the postthrombotic syndrome was avoided. Residual thrombus is associated with an increasing risk of postthrombotic syndrome. (J Vasc Surg 2012;■:■■■.)

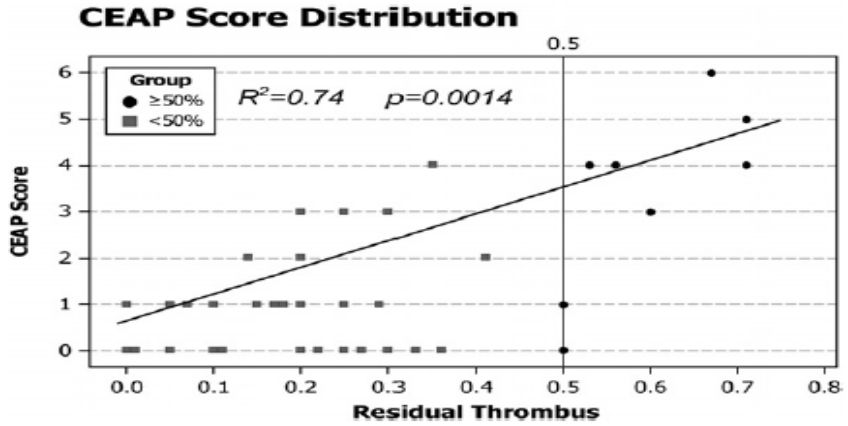
Study to evaluate correlation between residual thrombus and post-thrombotic syndrome (PTS)

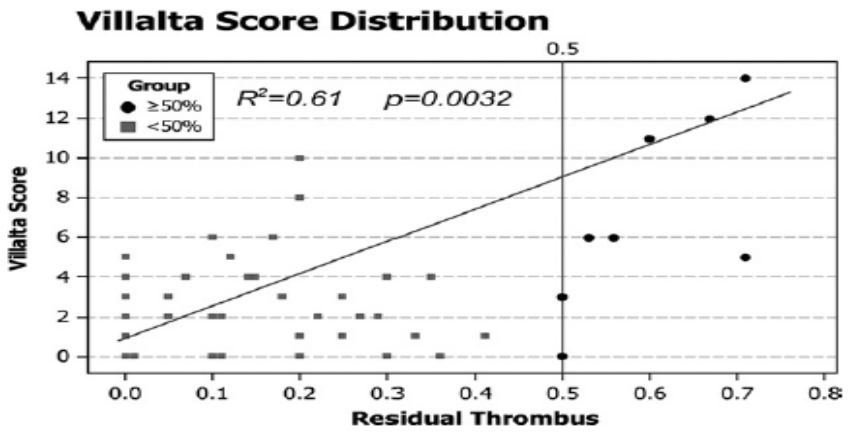
- 71 consecutive IFDVT patients treated with CDT
- Blinded comparison of pre- and post-treatment phlebograms and evaluation of CEAP/Villalta scores

Greater thrombus removal gives lower PTS rate

Comerota et al. J Vasc Surg. 2012 Mar;55(3):768-73.

Journal of Vascular Surgery®





First study to demonstrate:

- **Direct** and **significant** correlation of between PTS scores and thrombus clearance
- Conclusion: when thrombus clearance is complete, PTS can be avoided

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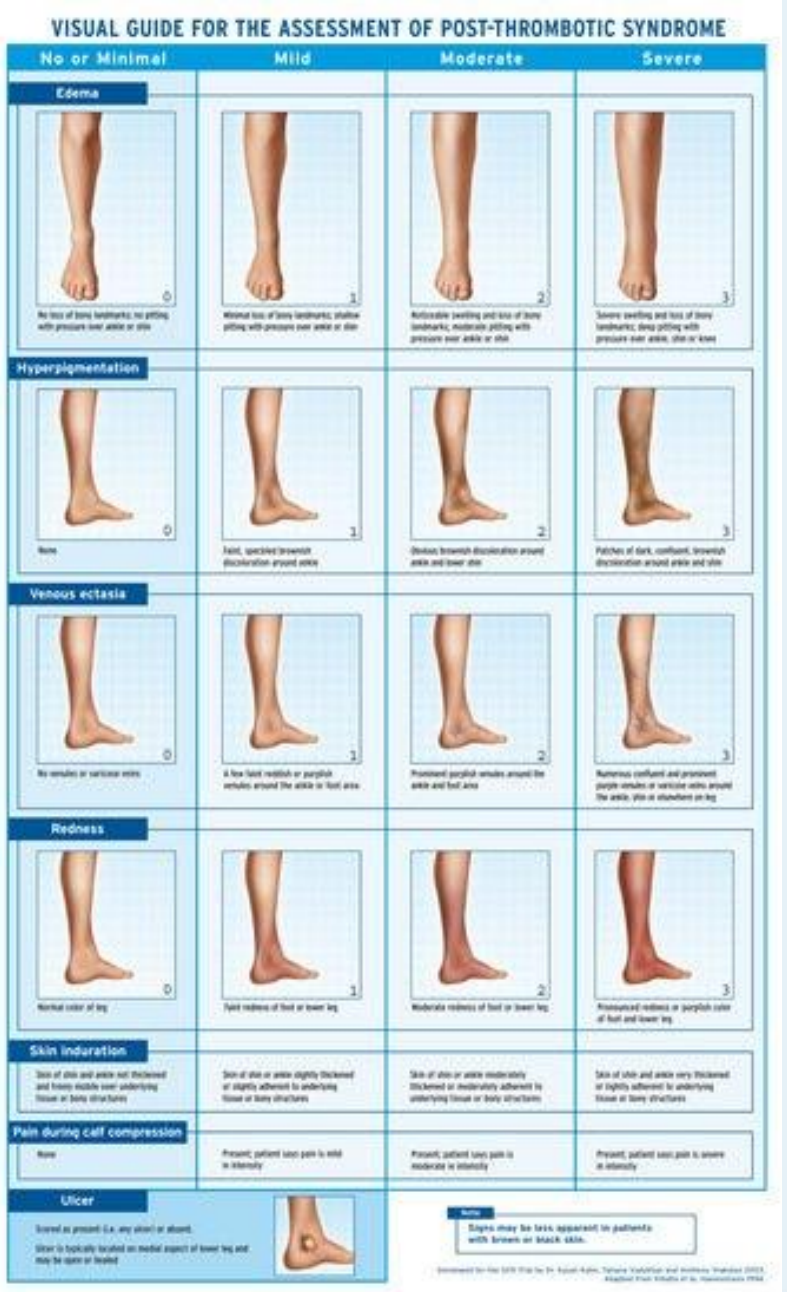
Villalta Score

Symptoms/clinical signs	*None*	*Mild*	*Moderate*	*Severe*
Symptoms				
Pain	0 points	1 point	2 points	3 points
Cramps	0 points	1 point	2 points	3 points
Heaviness	0 points	1 point	2 points	3 points
Paresthesia	0 points	1 point	2 points	3 points
Pruritus	0 points	1 point	2 points	3 points
Clinical signs				
Pretibial edema	0 points	1 point	2 points	3 points
Skin induration	0 points	1 point	2 points	3 points
Hyperpigmentation	0 points	1 point	2 points	3 points
Redness	0 points	1 point	2 points	3 points
Venous ectasia	0 points	1 point	2 points	3 points
Pain on calf compression	0 points	1 point	2 points	3 points
Venous ulcer	Absent			Present



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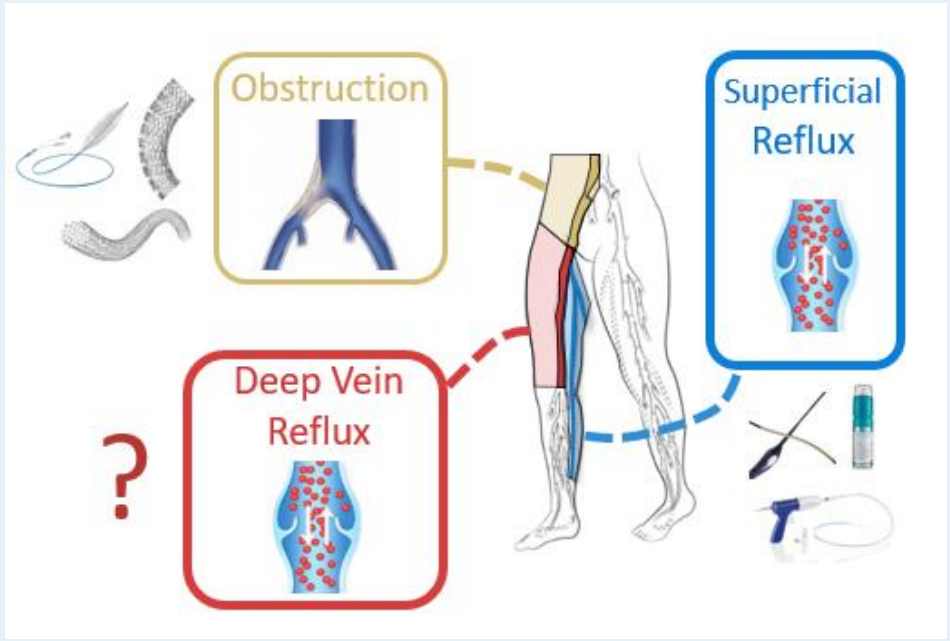
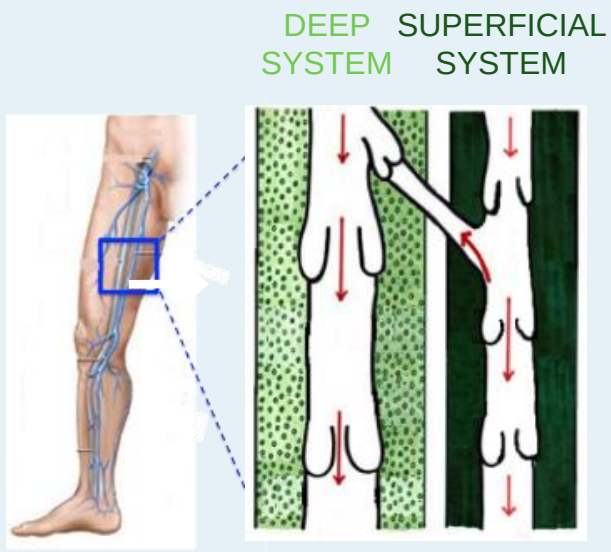
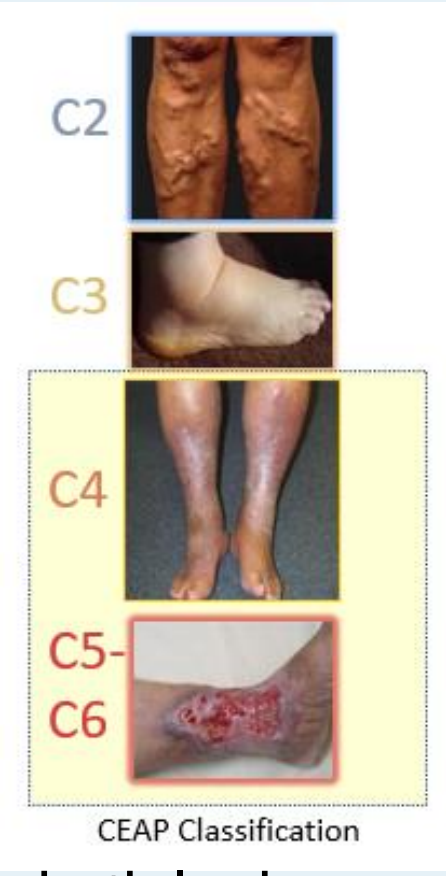
Three Major Underlying Causes of *Symptoms of Post-Thrombic Syndrome*





Diseased Refluxing Veins



CEAP Classification

'CVI' refers to *severe* Venous Disease (CEAP 4-6), where mixed etiologies are common including Deep Vein Reflux (DVR), Superficial Reflux, and Venous Obstruction. The most prevalent and progressive is *post thrombotic* after DVT

Post-Thrombotic Syndrome (PTS):Valve Destruction & Obstruction

The post thrombotic syndrome: Ignore it and it will come back to bite you

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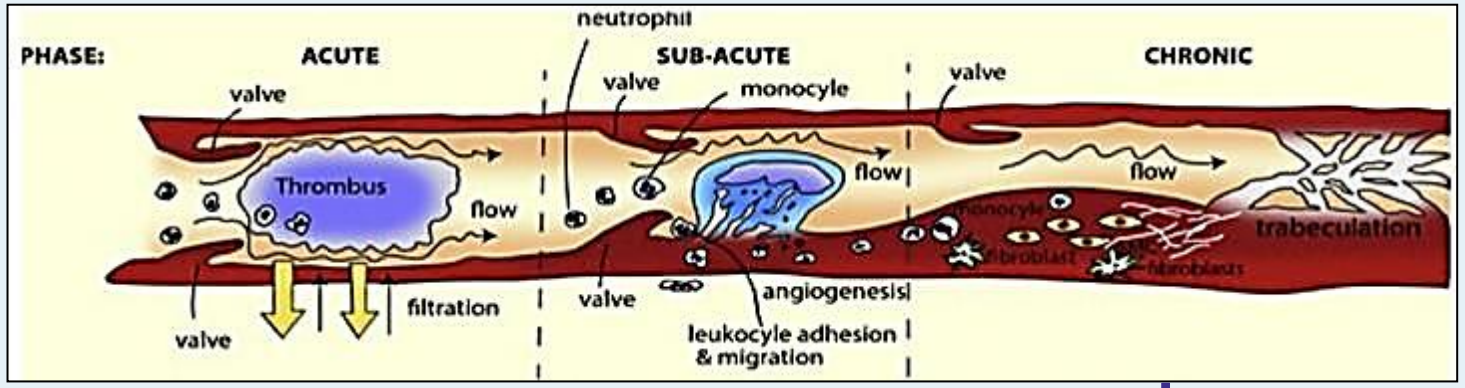
[a] Cardiovascular Center and Laboratory for Clinical Thrombosis and Hemostasis, Maastricht University Medical Center, Maastricht, the Netherlands
[b] Section of Vascular Surgery and the John Vascular Research Laboratory, Department of Surgery, University of Michigan School of Medicine, Ann Arbor, MI, USA



CVI CEAP Score Progression

Collagen scarring, trabeculae damage valves and cause obstruction

Most DVT Treatment Has Inadequate Outcomes

Isolated Iliac ± common fem: thrombectomy, stenting (ideal IDE cases)

– 20-30% Loss of Stent Patency at 3 years

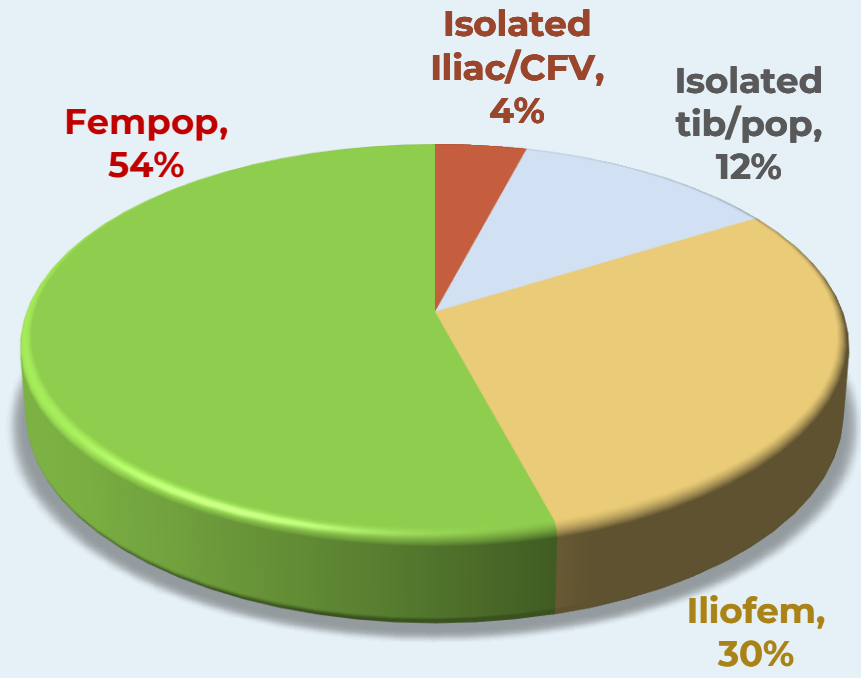
Isolated tibial and/or popliteal: Oral anticoagulants

Iliofemoral: Thrombectomy, iliac stenting, ill defined inflow

– PTS rates of 44% (18% moderate-severe) in first 2 years[1]

Femoral: ATTRACT- intervention not supported by risk-benefit

– PTS rates of 41% (17% moderate-severe) in first 2 years[2]



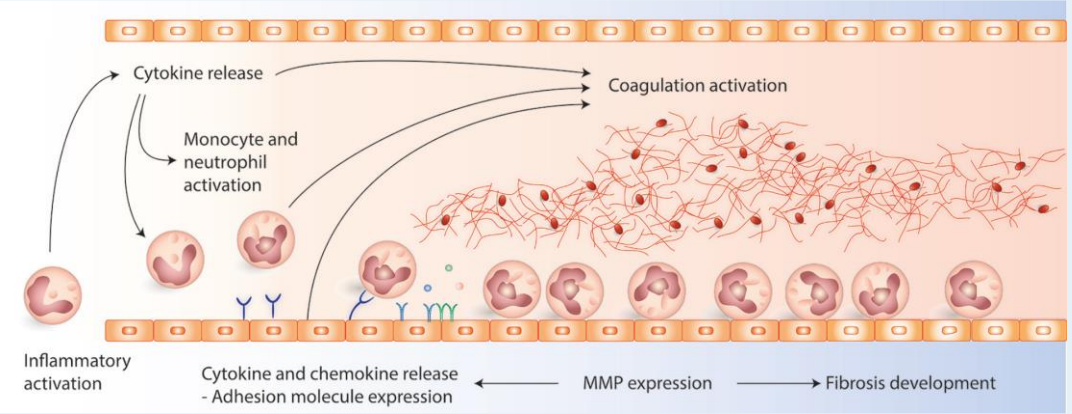
Anatomical data from 1,338 patients in **De Maeseneer, et al.** *Eur J Vasc Endovasc Surg* (2016) 51:415-420

1. **Comerota et al.** *Circulation.* 2019;139:1162.
2. **Kearon et al.** *Thromb Haemost* 2019;119:633.

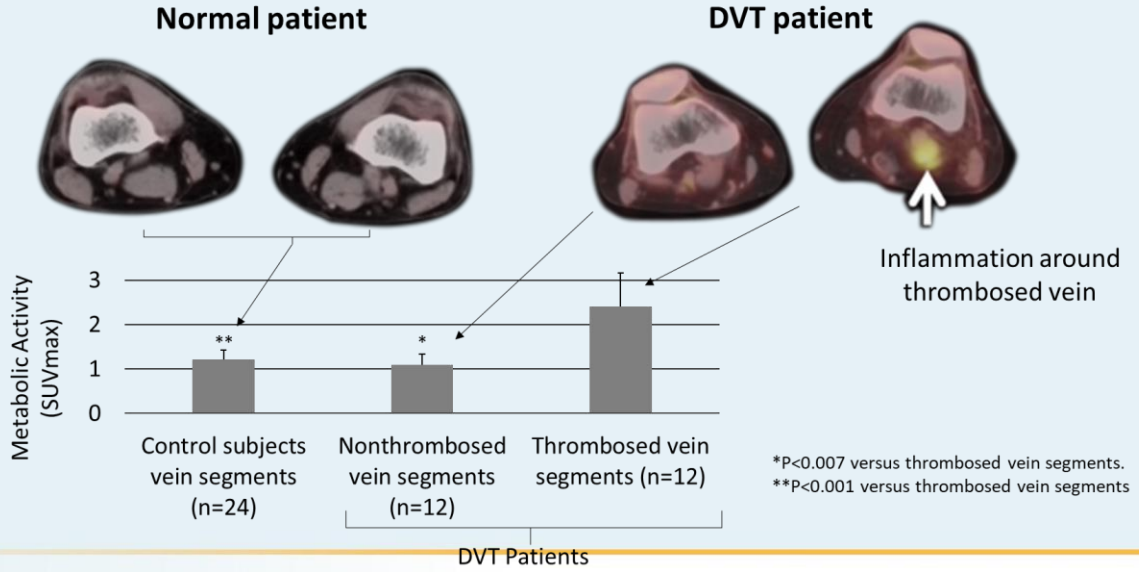
Why are Outcomes Inadequate?

- Current DVT therapies are limited to methods of clearing thrombus to provide an acute outcome
- Post thrombotic syndrome (PTS) remains a long-term outcome in 30-50% of patients, regardless of thrombus clearance method
- Current PTS therapies include…
  - Anticoagulation
  - Compression stockings
  - Encourage ambulation
  - PTA/Stenting of residual obstruction
  - Access PTS Trial utilizing TPA with adjunctive PTA/Stenting
- Preventing PTS requires addressing the underlying causes (inflammatory hypothesis?)
  - Chronic vein wall changes/fibrosis
  - Damaged/dysfunctional valve

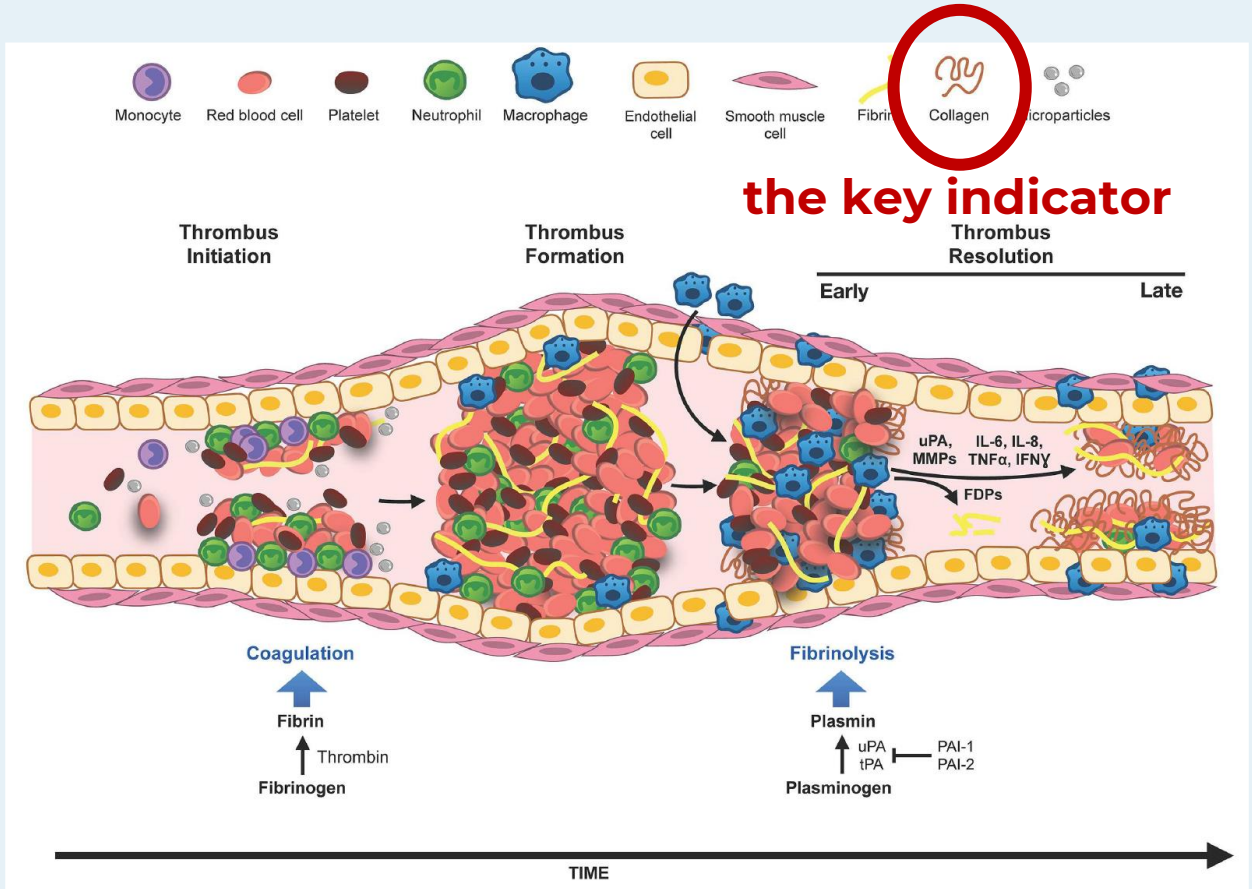
Inflammation is Critical in DVT Formation and Resolution



Mosevoll, et al. *Front. Med* 5:147.



Rondina, et al. *Clin Nucl Med.* 2012 Dec;37(12):1139-45.



"**Resolution of inflammation** and acceleration of this process is believed to be beneficial for restoring vein wall patency and reducing the pathology associated with PTS."

Mukhopadhyay, et al. *Frontiers in immunology*. 2019;10:1348.

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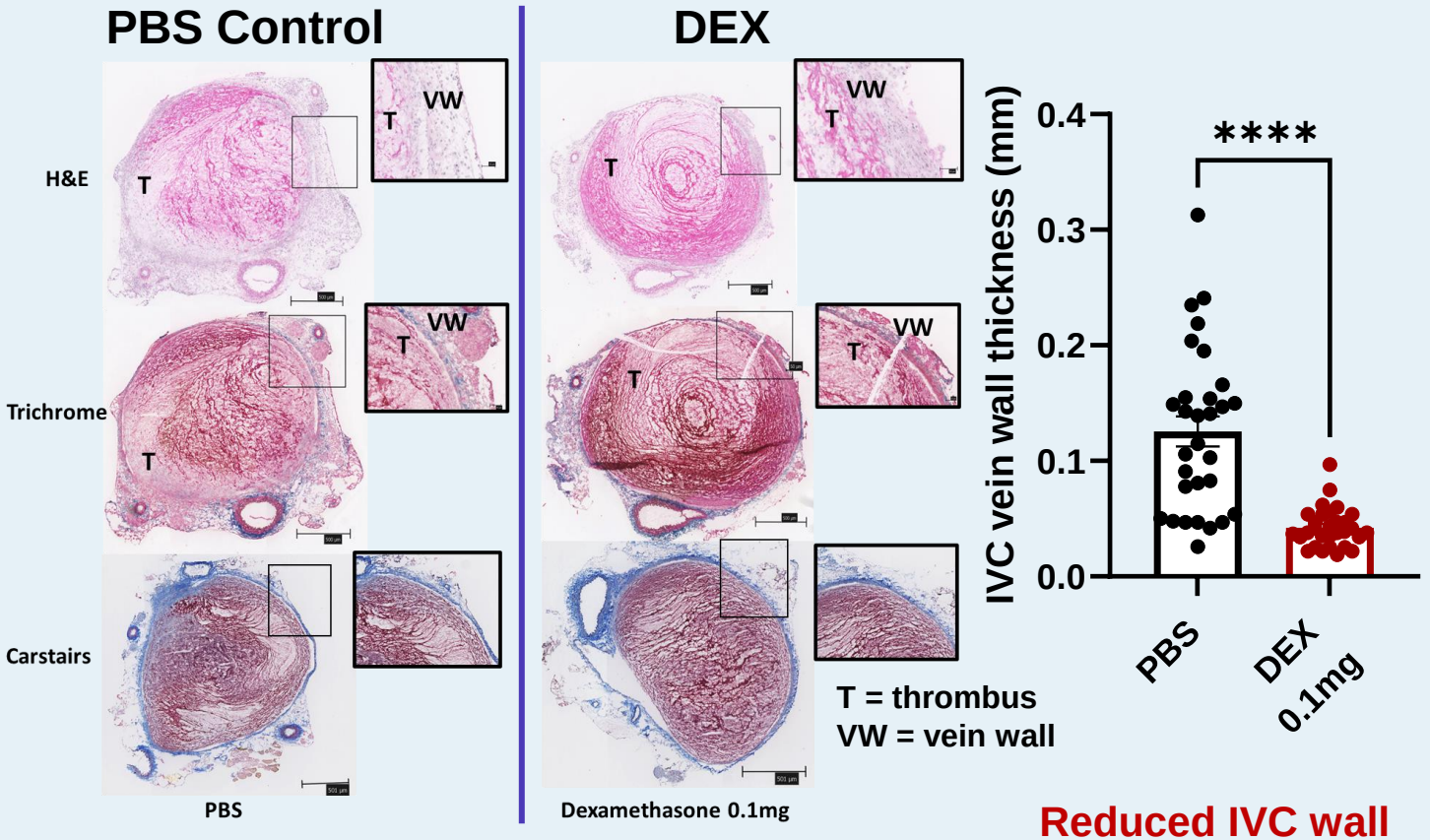
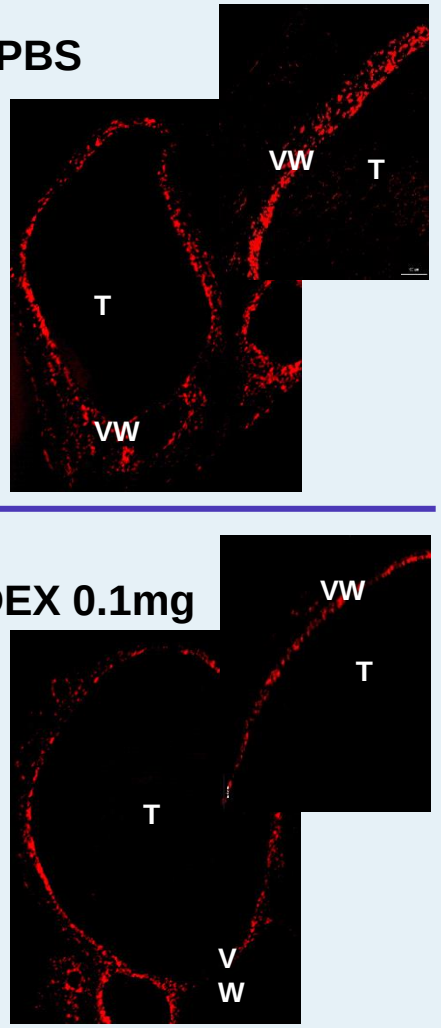
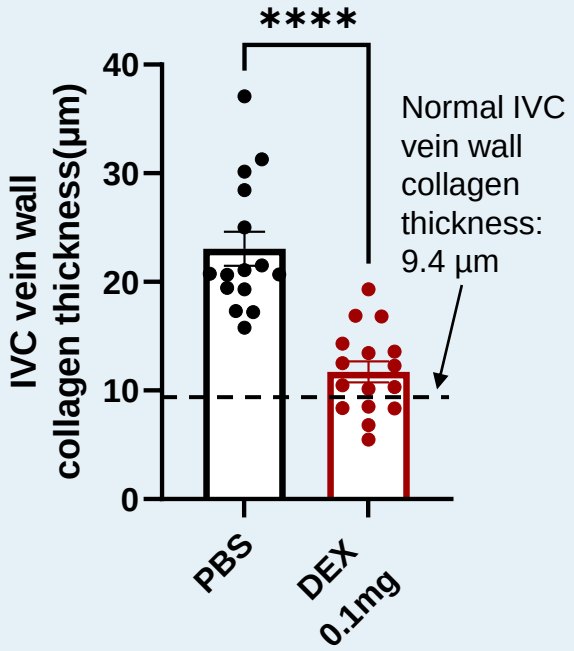
Preclinical Mouse Studies with Dexamethasone



T = thrombus
VW = vein wall

Reduced IVC wall thickness by 70%



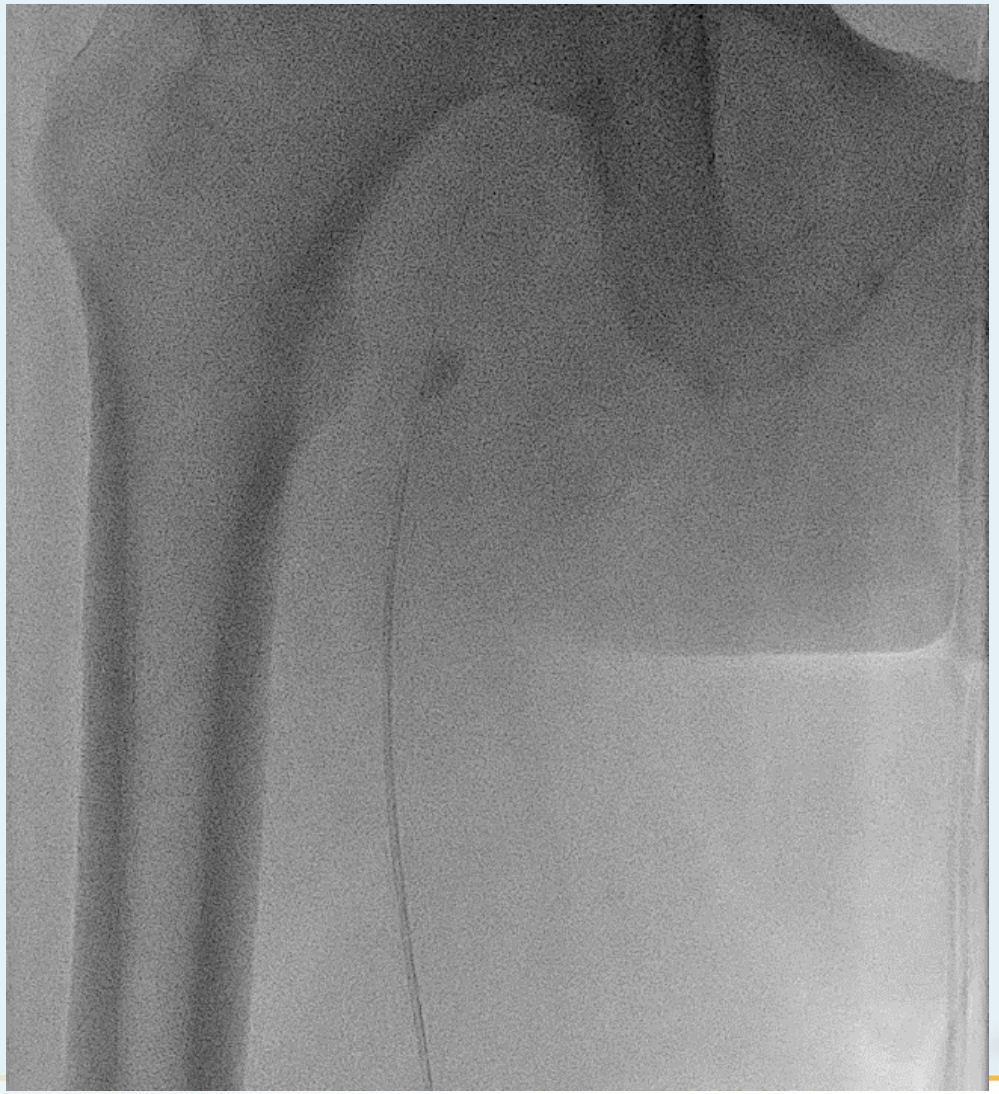


Average collagen thickness with DEX approaches normal IVC

n= 16 mice per group. Scale 500µm.
*****p<0.001.**
******p<0.0001.**

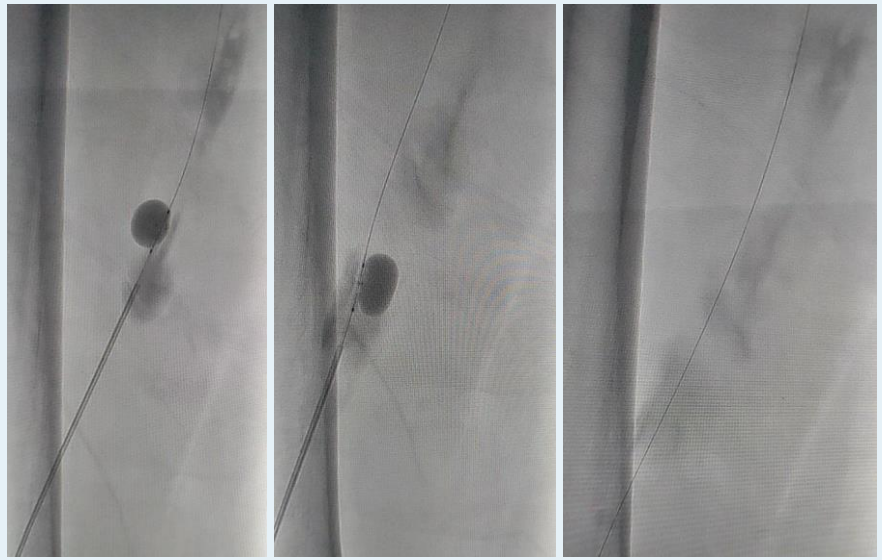
Vijay, A. AVF2023: ***Mouse model of IVC ligation at Day 0, deligation and drug delivery at day 2, sacrifice at Day 8***

Reducing DVT Inflammation post-Recanalization with Targeted Dexamethasone Delivery

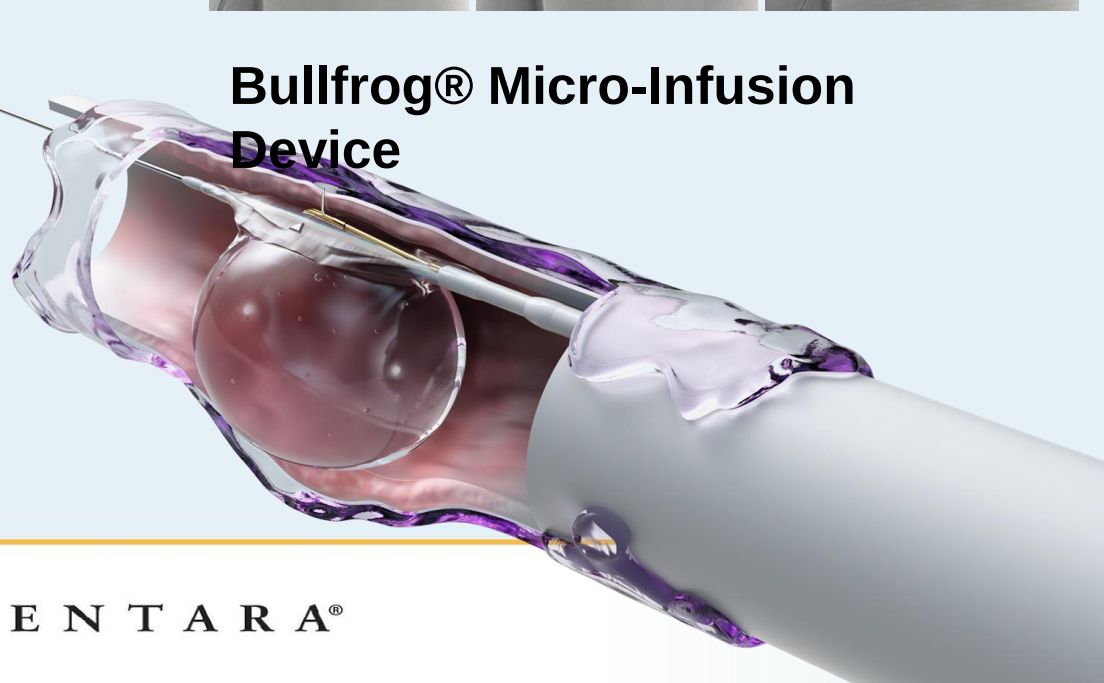


<u>Workflow</u>:

1. **Open the lumen**
2. **Treat the vein**
3. **Stent as needed**



Bullfrog® Micro-Infusion Device



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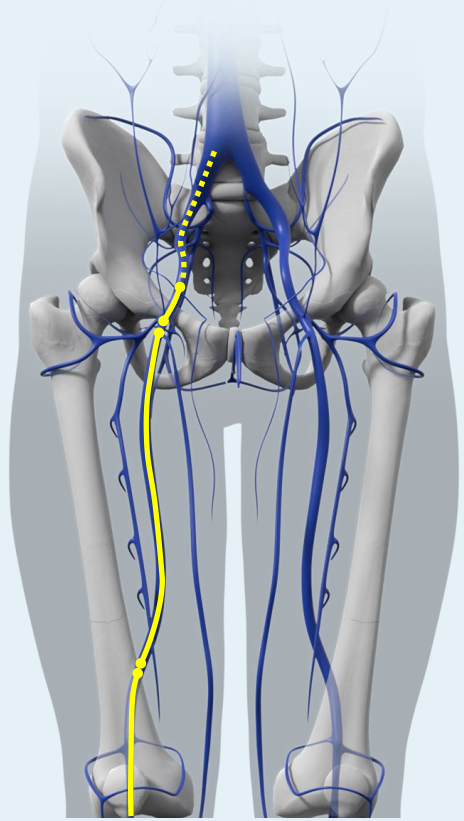
DEXTERITY-AFP Trial Design

DEXTERITY-AFP: Perivenous **DEX**amethasone Therapy: **E**xamining **R**eduction of **I**nflammation after **T**hrombus Removal to **Y**ield Benefit in Acute Femoropopliteal (AFP) DVT

Global co-PIs: David Dexter and Mahmood Razavi

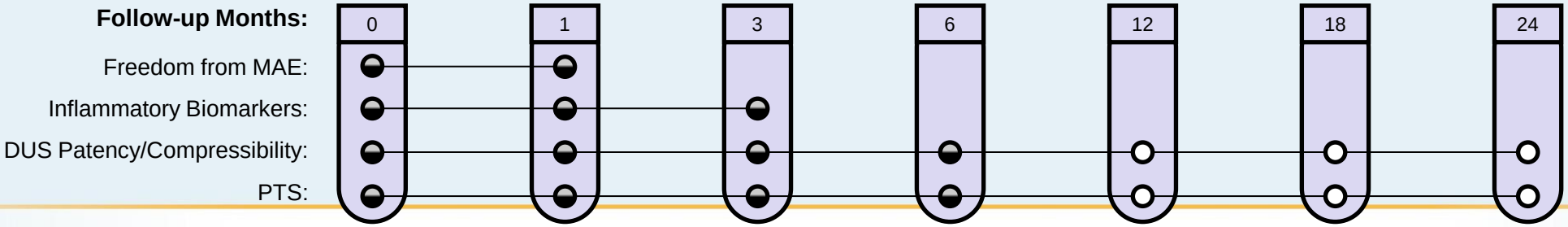
Principal Inclusion Criteria: 0-14 days post symptom onset, involvement of common femoral, femoral, or popliteal veins



Procedure: ± Lysis | ± Thrombectomy | + Drug Delivery | ± Venoplasty | ± Stenting

Open-Label Phase: **20 patients** All receive dexamethasone

(followed by) **Dual-blind RCT:** **30 patients** Dexamethasone | **30 patients** Saline placebo



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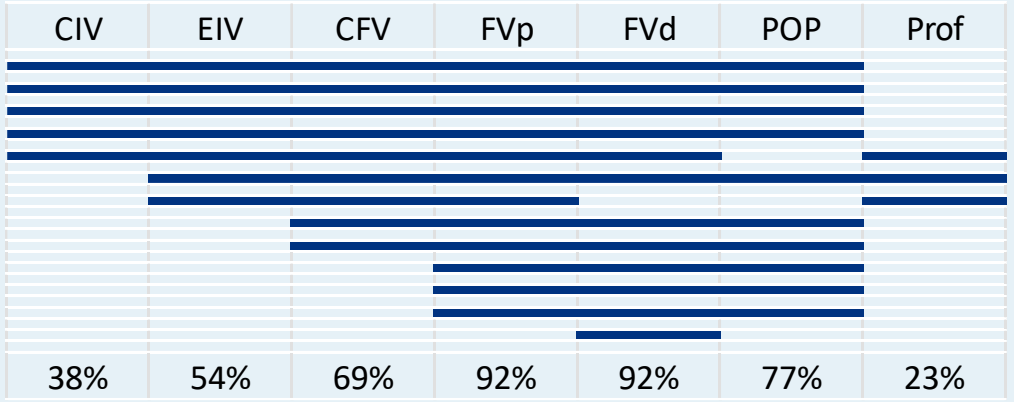
DEXTERITY-AFP First 13 Participants

Participant Characteristic	N (%) or Mean ± S.D.
Enrolled prior to 12/31/2022	13 (100%)
Withdrawn after 1 mo f/u	1 (7.7%)
Age	55 ± 16
Male gender at birth	10 (76.9%)
Left side DVT	10 (76.9%)
Days post symptom onset	8.9 ± 4.2
BMI	29.7 ± 3.9
Office BP	136 ± 17 / 80 ± 10
Follow-up	**N (%) or Mean ± S.D.**
Months of follow-up	9.6 ± 4.3
Drug- or device-related SAE	0 (0%)

Treatment Characteristics	N (%)
Thrombolysis	8 (61.5%)
Thrombectomy	12 (92.3%)
Stenting	7 (53.8%)
Vein Length Targeted with Dexamethasone	35 ± 12 cm
Dexamethasone Perivascular Dosage	46 ± 15 mg

Extent of DVT by Participant:



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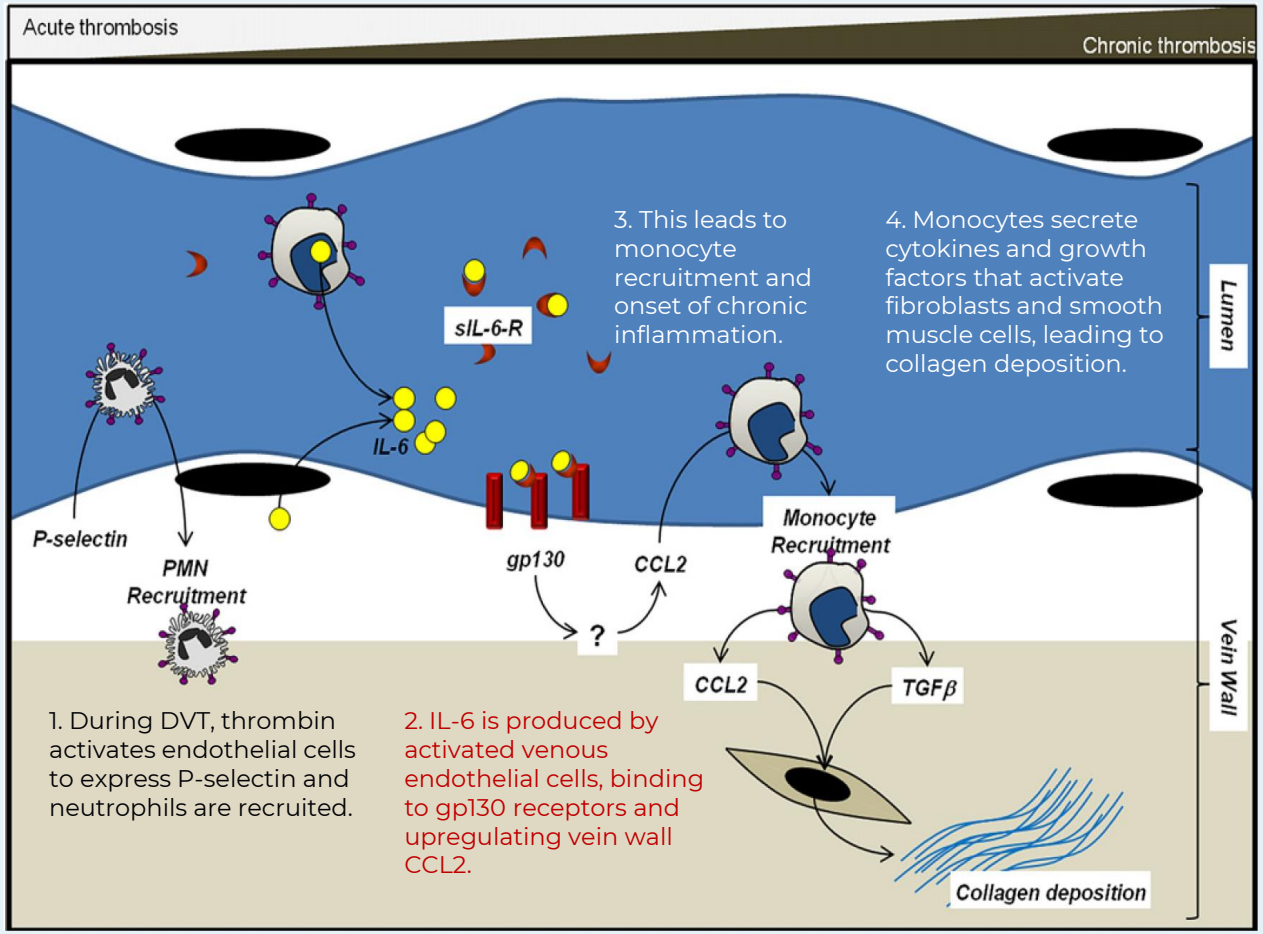
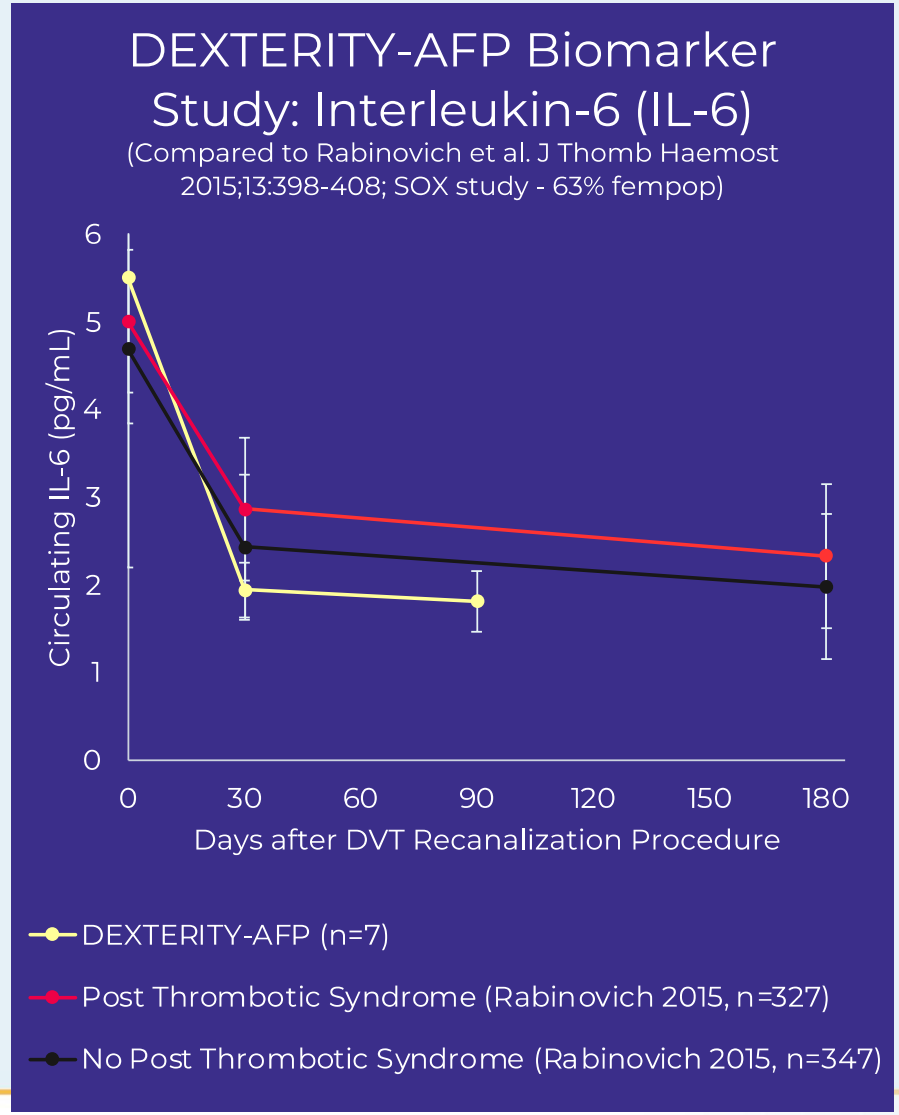
DEXTERITY-AFP Early Biomarker Examination

IL-6: An Upstream Inflammatory Marker



From Wojcik, et al. Ann Vasc Surg 2011;25:229-239.



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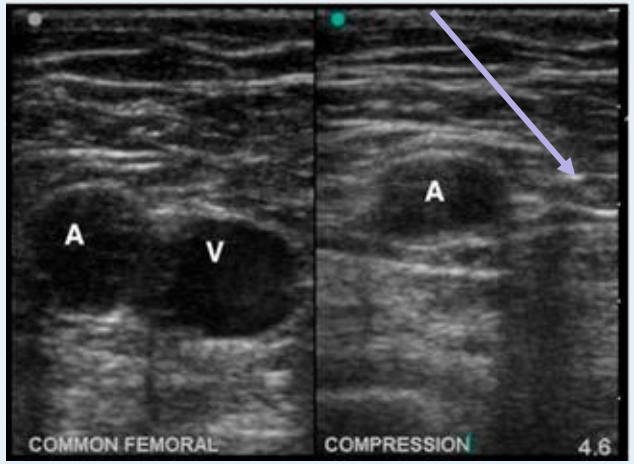
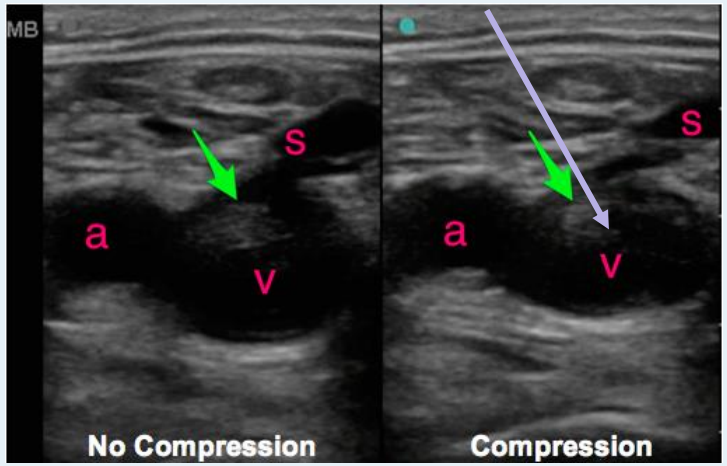
DEXTERITY-AFP Early Ultrasound Examination

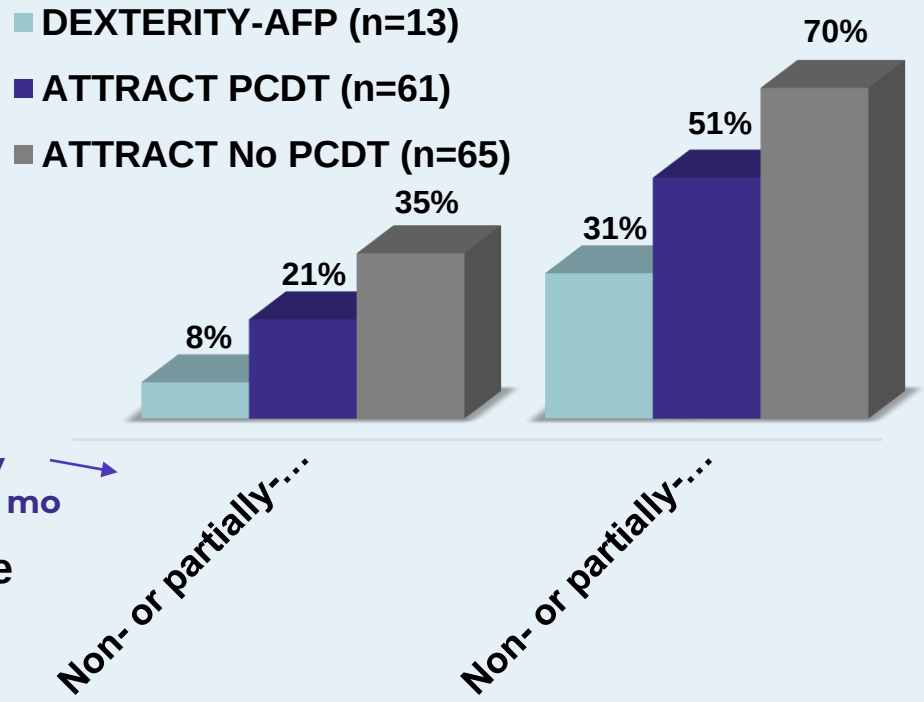
Normal vein:
Fully compressible (FC)



Thrombosed vein:
Non-compressible (NC)



DEXTERITY-AFP Preliminary Data: 1-month DUS Compressibility



Non-compressibility of the CFV at 1 month is predictive of poor chronic outcomes*

higher rates of **any PTS at 2 years**
FC: 46%
NC: 61%
p < 0.001

worse **Quality of Life Score** at 2 years**
FC: 81.4
NC: 73.2
p = 0.004

higher **moderate-severe PTS at 2 years**
FC: 19%
NC: 30%
p = 0.003

*Weinberg et al. Vasc Med. 2019 Oct;24(5):442-451

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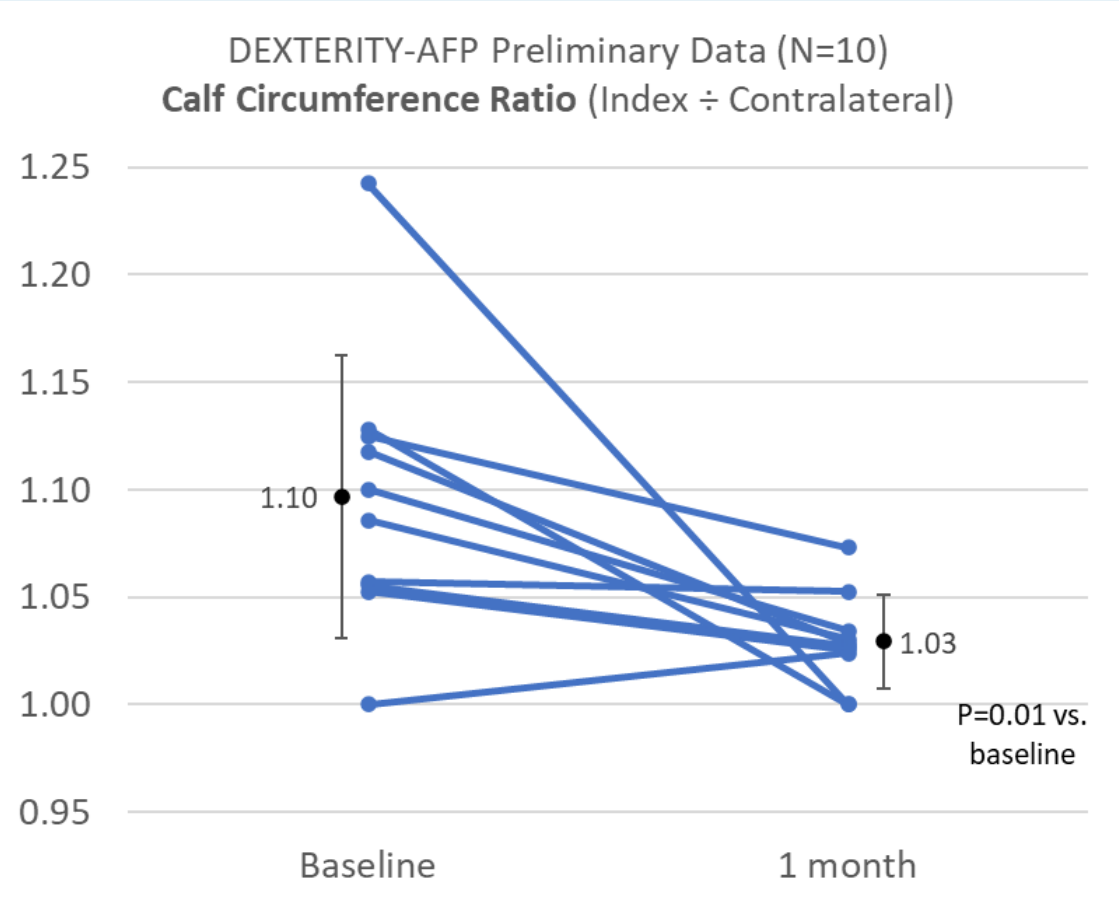
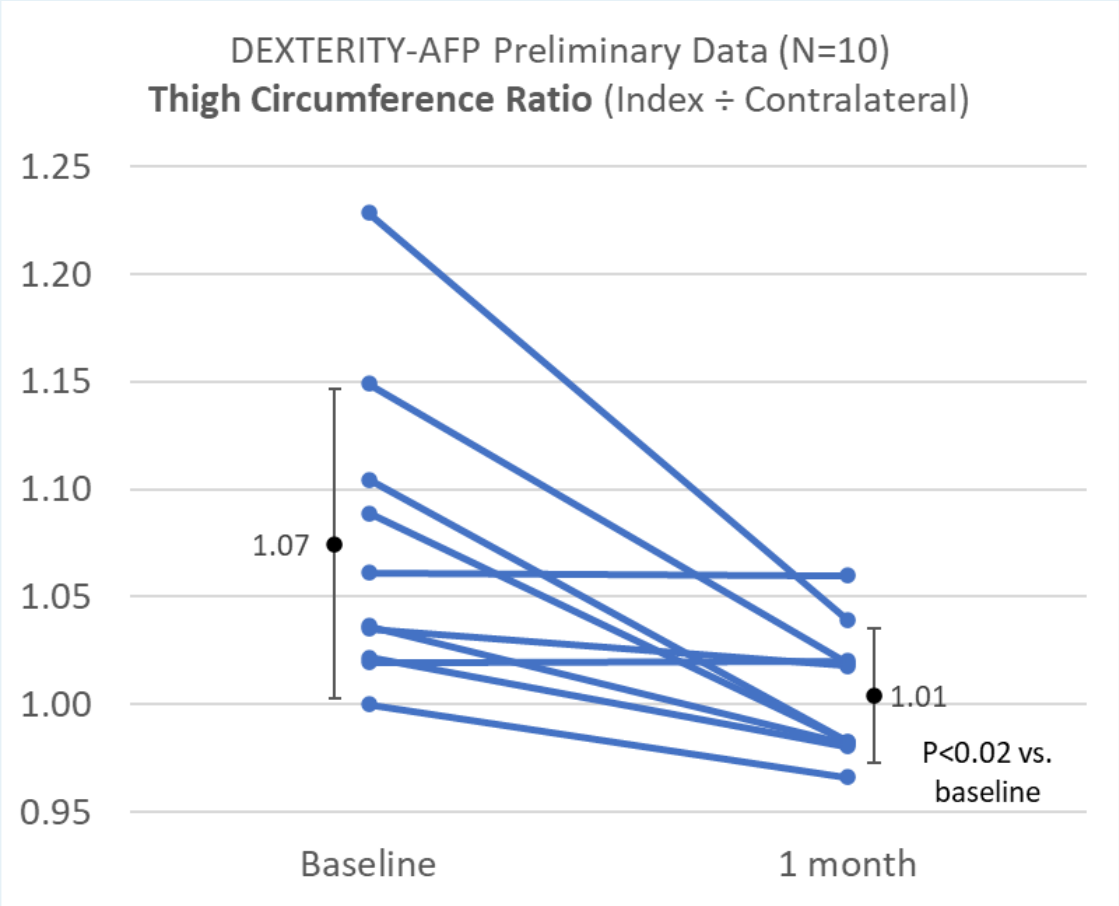
DEXTERITY-AFP Early Leg Circumference Examination





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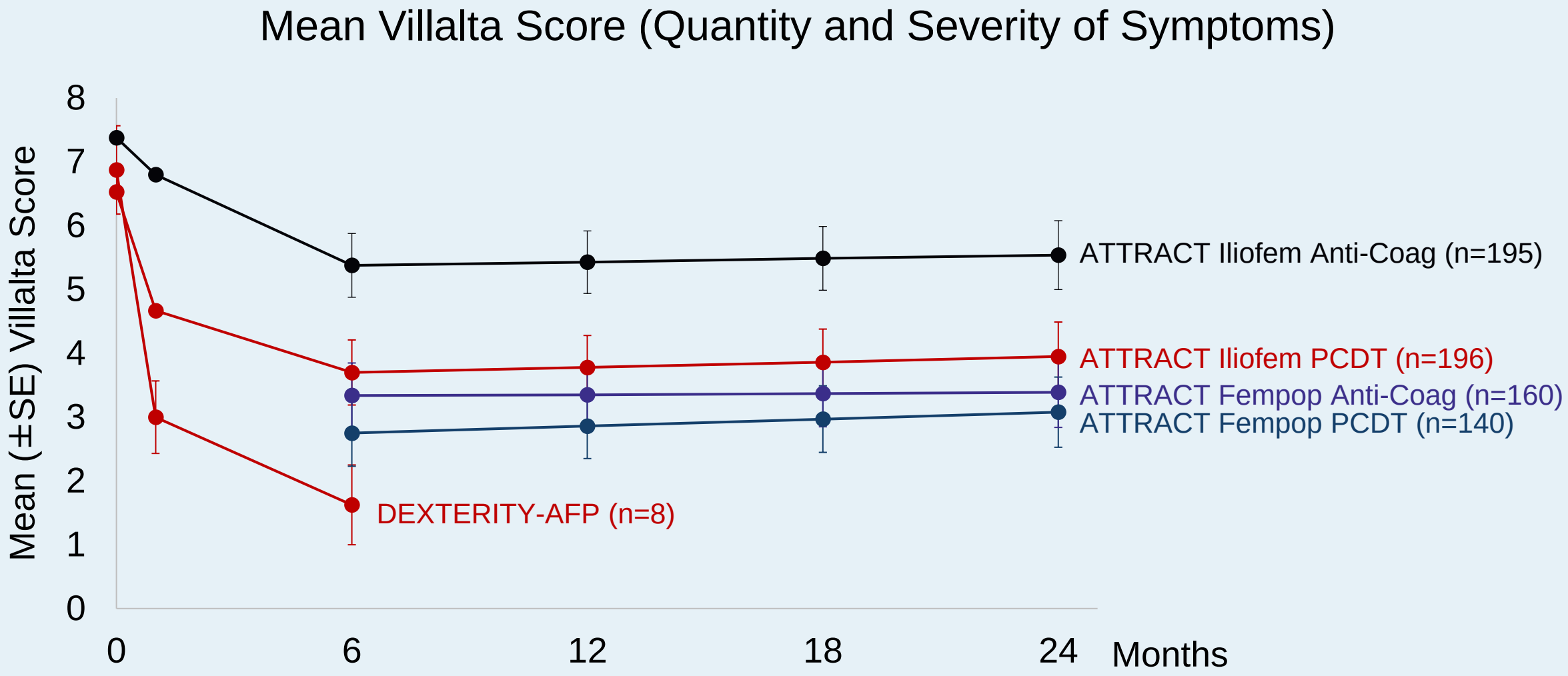
DEXTERITY-AFP Preliminary Villalta Score Examination



Comerota, et al. *Circulation.* 2019;139:1162–1173.
Kearon, et al. *Thromb Haemost.* 2019;119:633-644.

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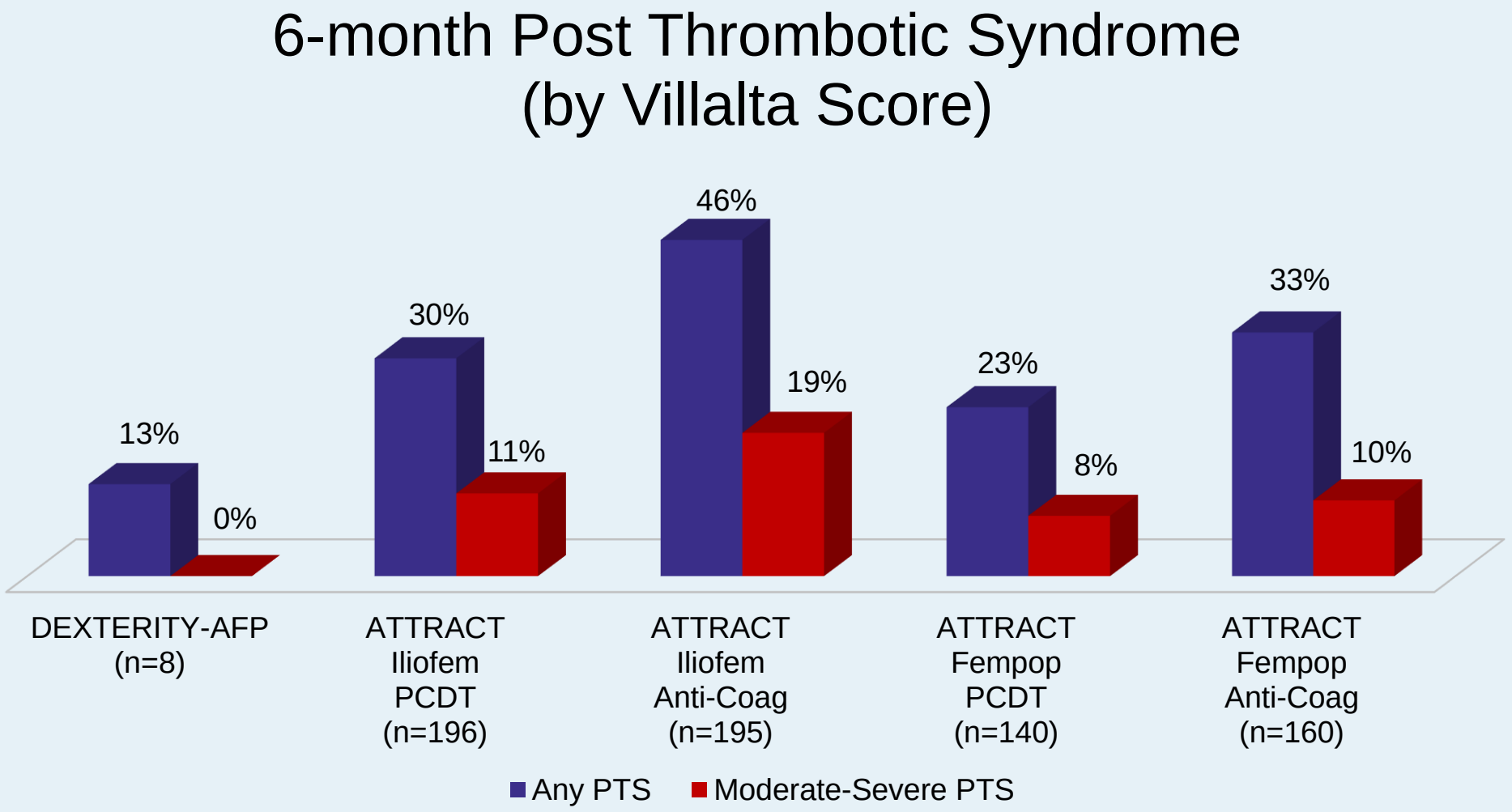
DEXTERITY-AFP Preliminary PTS Examination



Comerota, et al. *Circulation.* 2019;139:1162–1173.
Kearon, et al. *Thromb Haemost.* 2019;119:633-644.

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Summary of Early DEXTERITY-AFP Outcomes

- DVT continues to have poor outcomes, and aggressive thrombus removal alone may not help
- The anti-inflammatory treatment of underlying venous inflammation is possible with localized perivascular drug delivery
- Dexamethasone in preclinical studies appears to normalize vein wall in the presence of DVT
- Preliminary biomarker, compressibility, and Villalta signals all appear promising from the initial participants enrolled in study

Interventional Management of Chronic Obstruction

2
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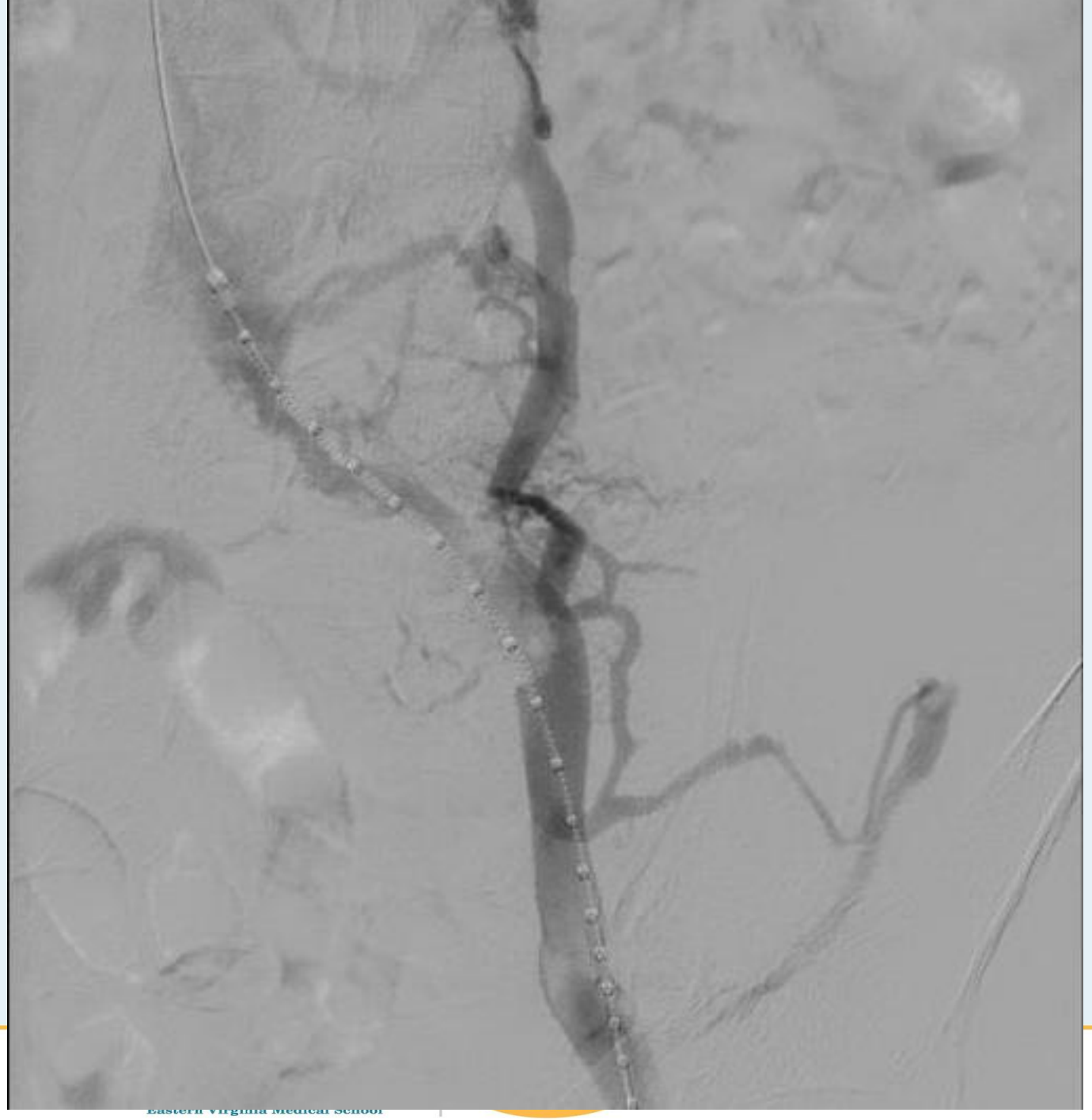

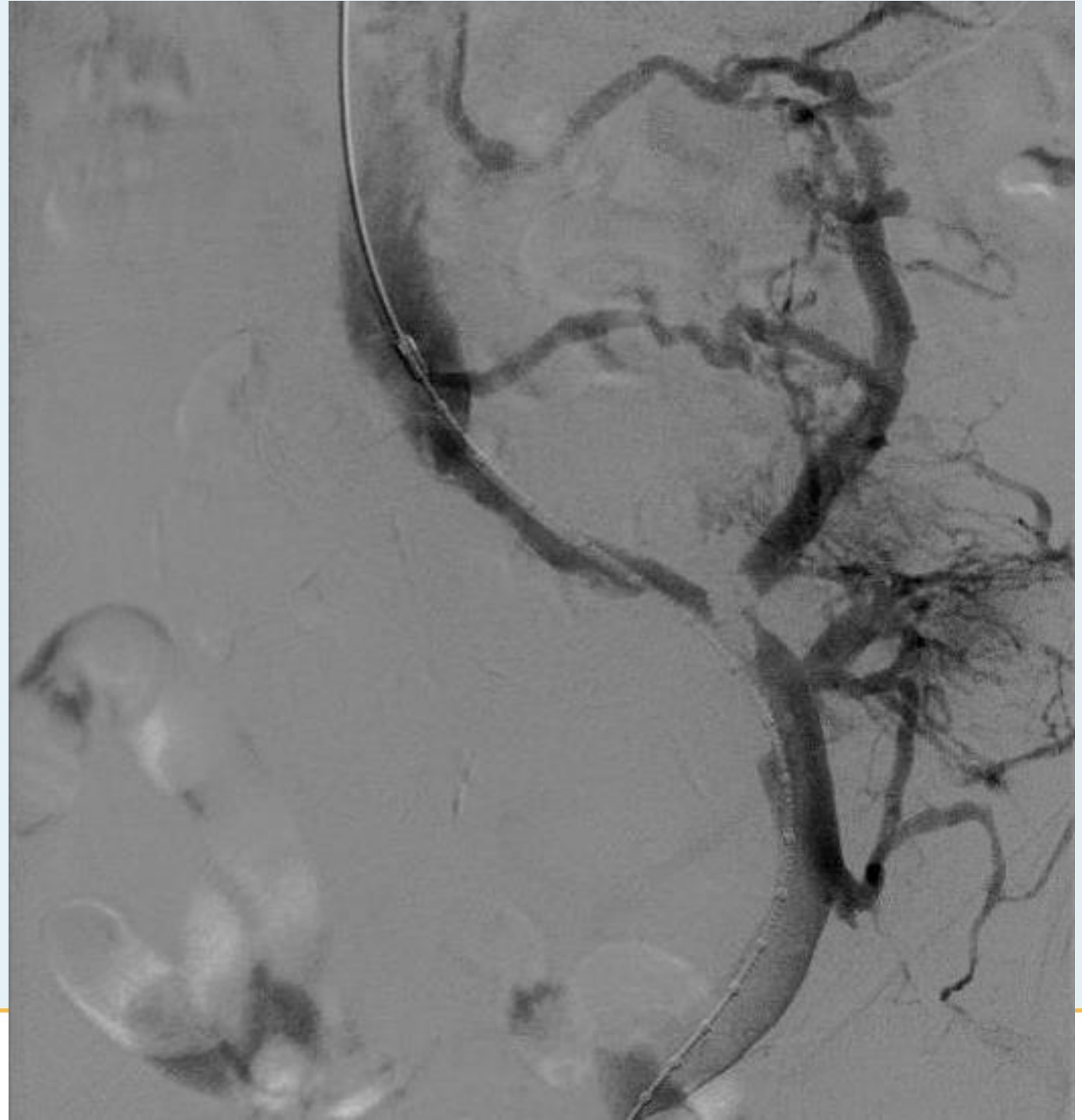

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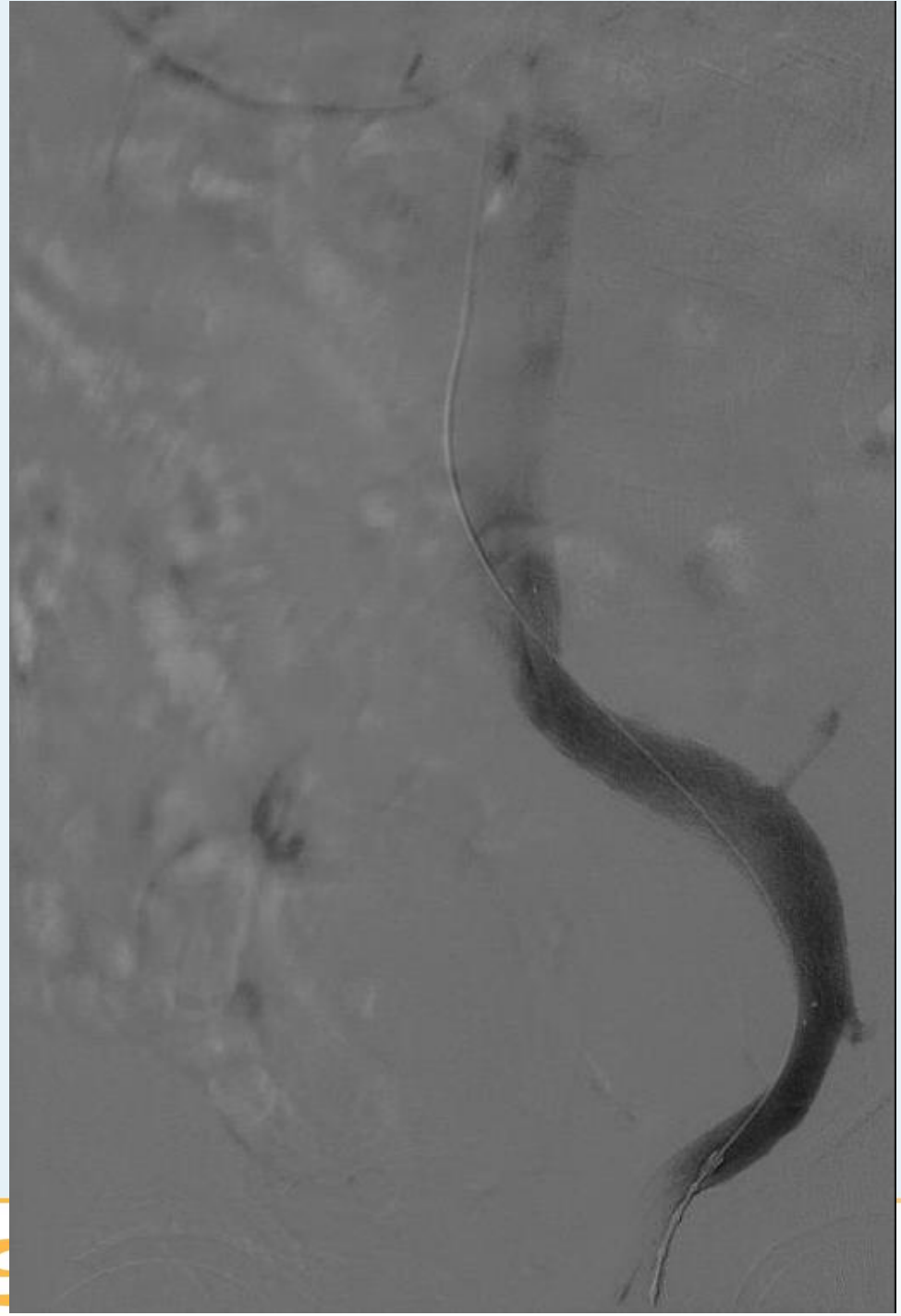
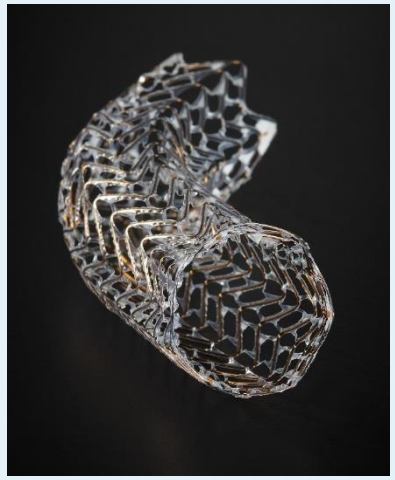


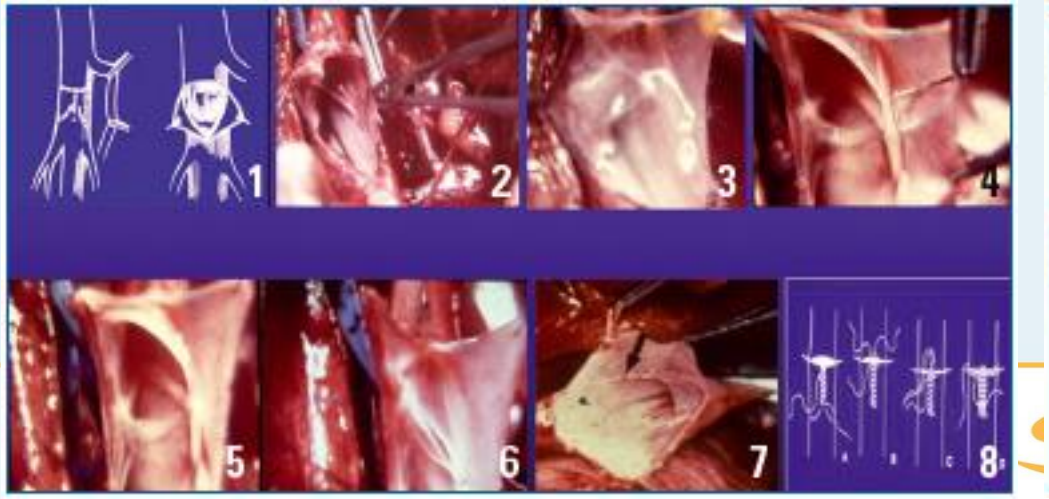
IVC and Iliac Vein Obstruction

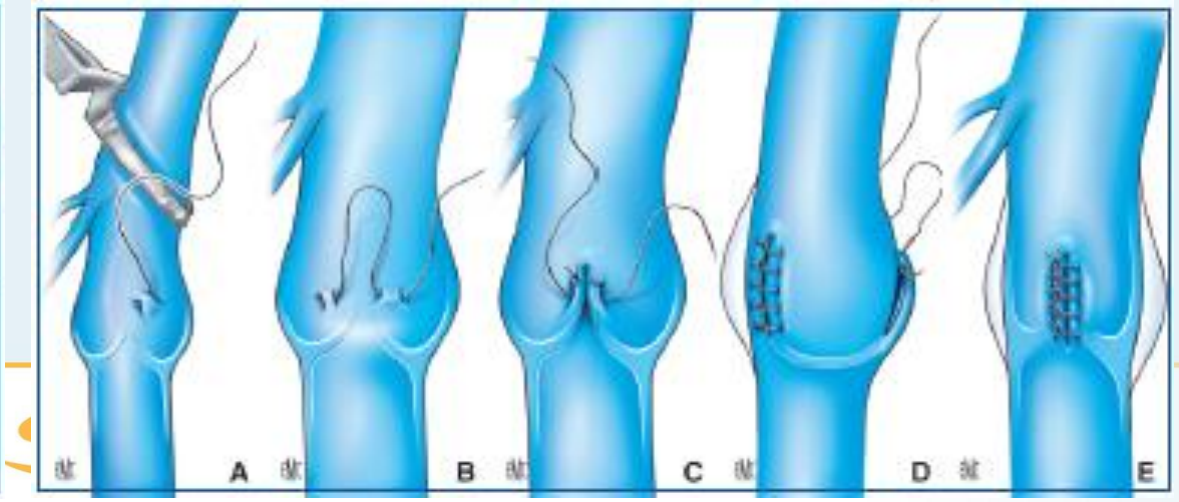
Current stents are useable from the CFV to the Terminal IVC
New Stents are being investigated for IVC obstruction



Can We Treat Reflux?

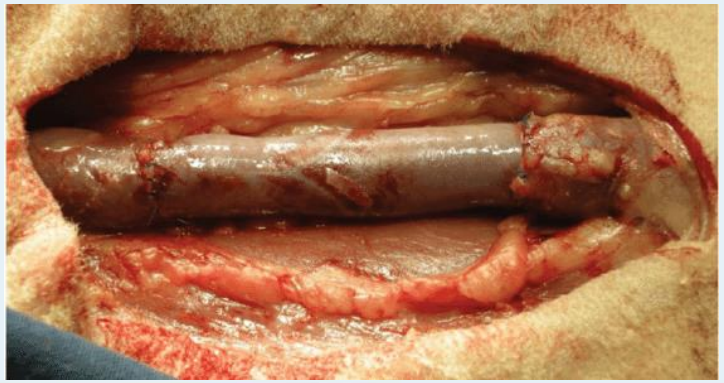
- The valve can be primarily repaired
- Kistner 1968 performed the first valvuloplasty
- In internal valvuloplasty, the vein is opened and the valve is identified under direct visual control
- In external valvuloplasty, the vein is repaired without opening

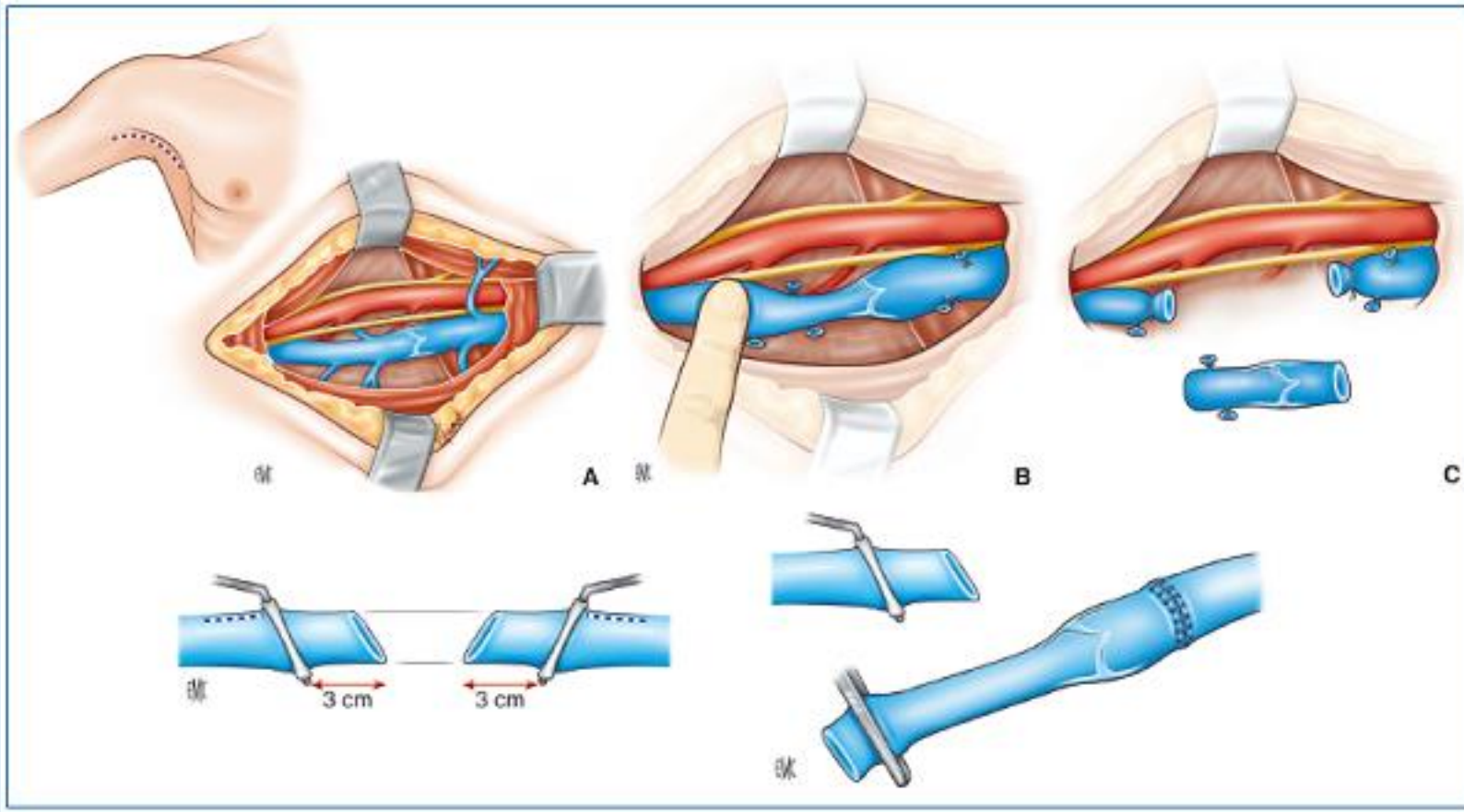




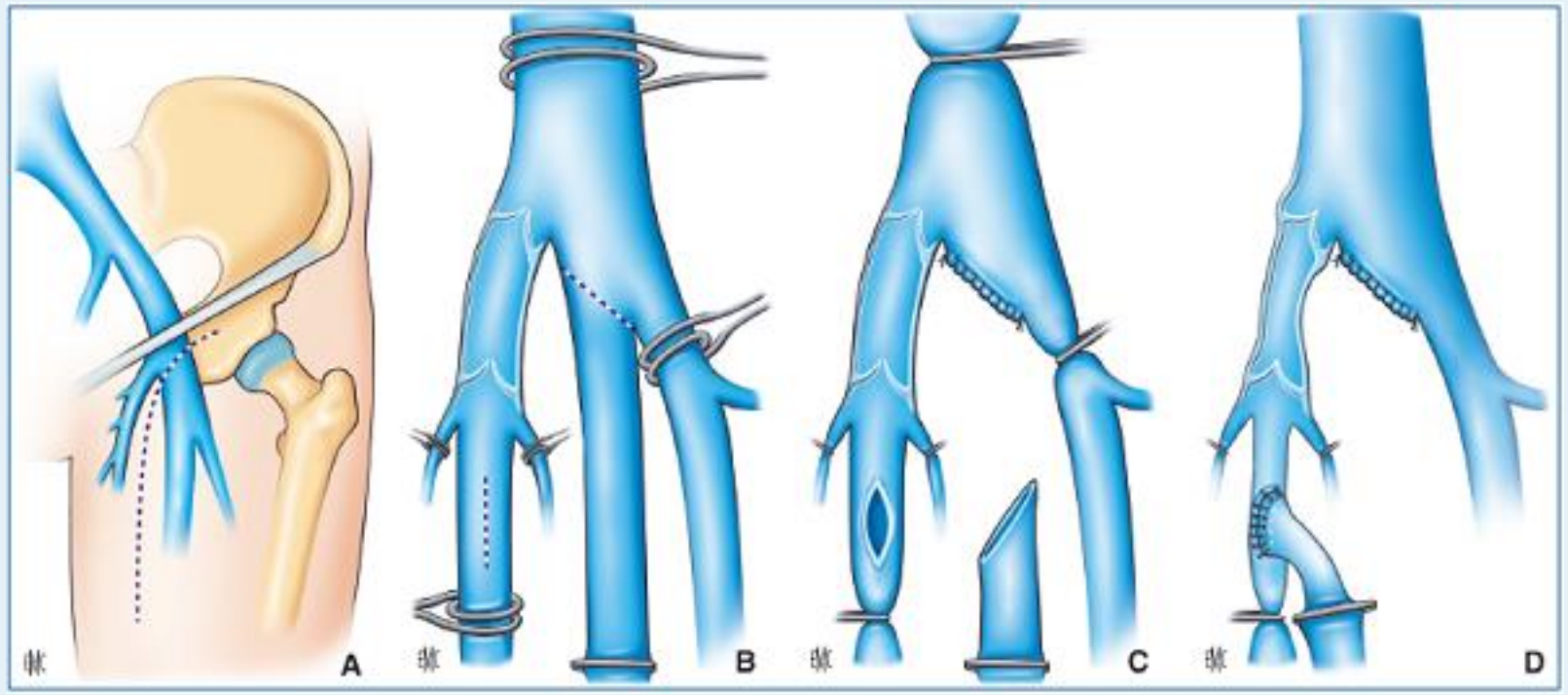
Venous Valvular Transplantation

- Transplantation of a venous valvular segment. In 1982, Taheri (USA) and Raju (USA) proposed using the humeral and axillary veins which have a functional valve and can be collected undamaged and transplanted into the lower limb



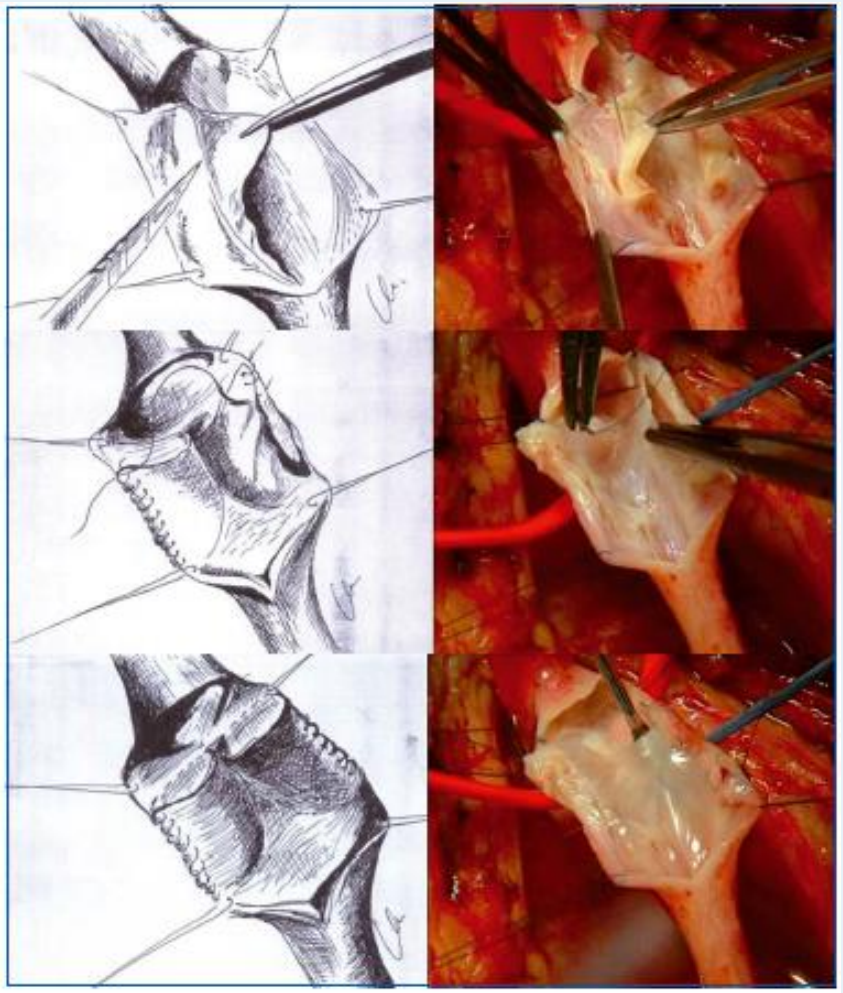


Venous Valve Transposition



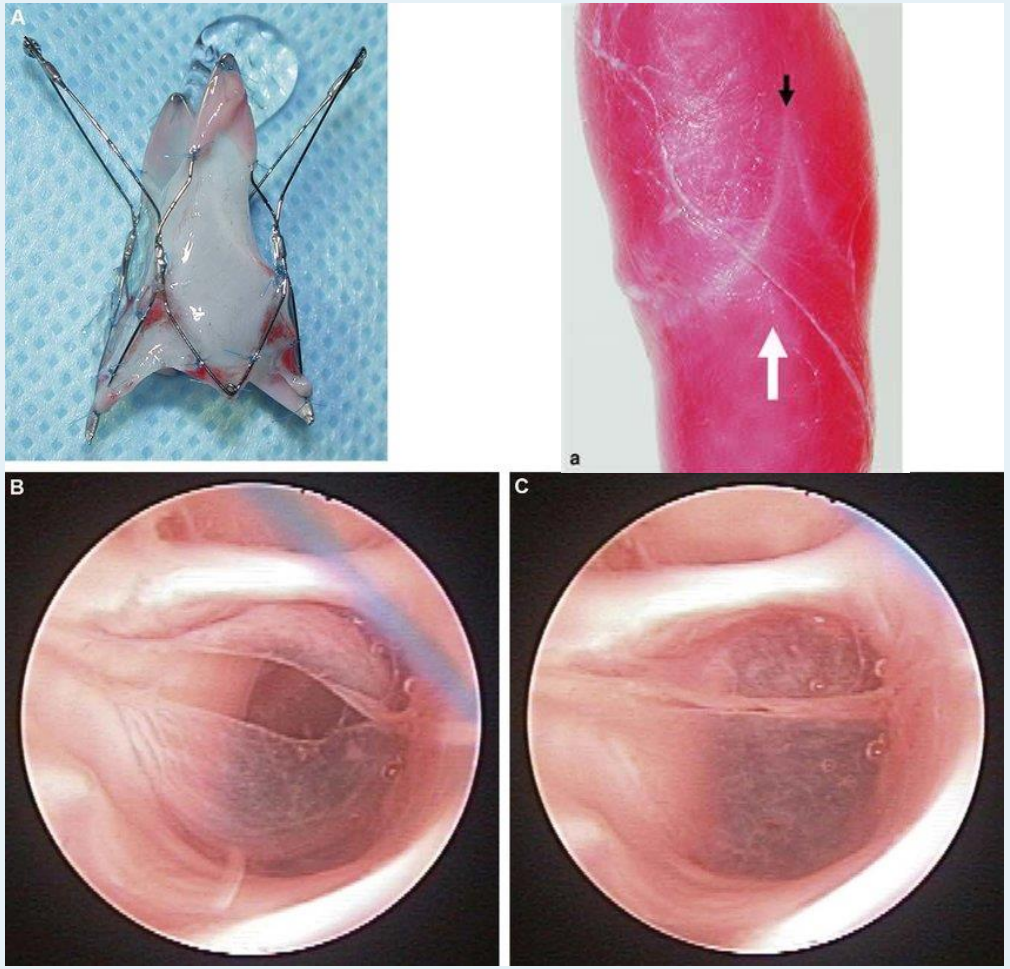
- Transposition consists of transposing the vein that is the site of reflux onto another lower limb vein, below its competent valve). R. Kistner (USA) invented this technique in 1982.

Neo-Valve Creation



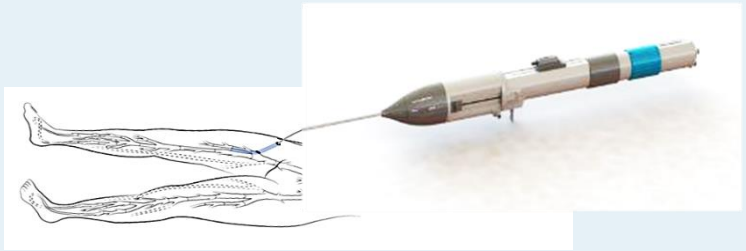
- The creation of a neovalve using venous tissue from the patient was proposed by P. Plagnol (France) in 1999 and by O. Maleti
  – *After opening the vein a few centimeters along its axis, the operator divides its wall on one side into two layers.*
  – *This detachment stopped in the middle allows construction of a sac which corresponds to a valve in a normal subject.*
  -The same technique is performed on the other side thus creating a valve with 2 valvular cusps.(Italy) in 2002.

Percutaneous Autologous Valve Transplant

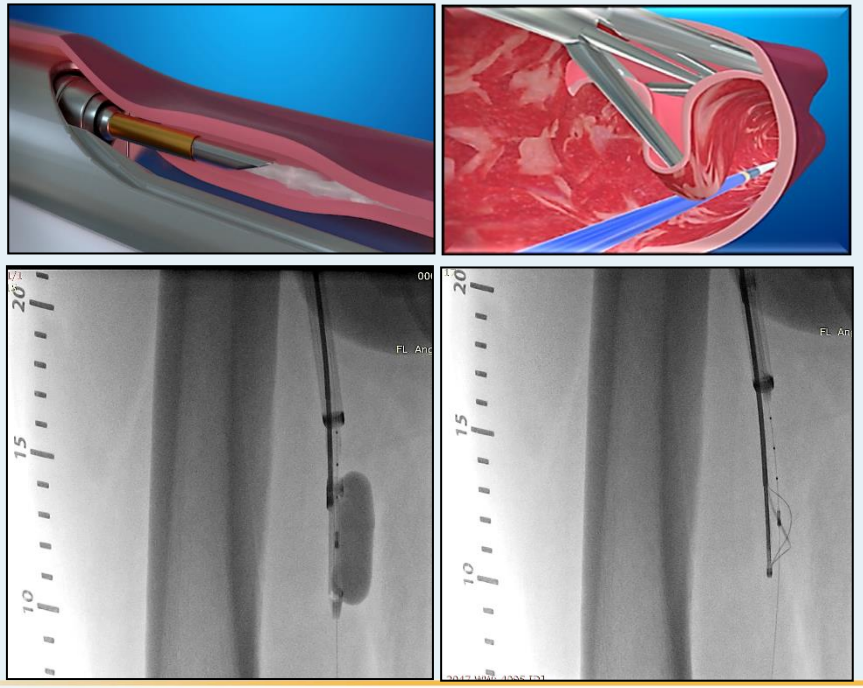


- Percutaneous autologous venous valve transplantation. (A) The harvested autologous venous valve attached to a stent valve template. (B) Venoscopy of the transplanted valve specimen at 3 months. Bicuspid valve inside a flow model demonstrates thin leaflets in the open position and (C) closed position.

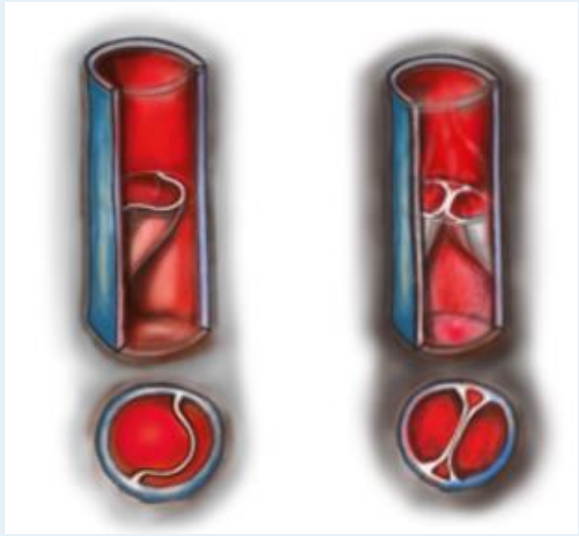
Overview of BlueLeaf and EVF (Endovenous Valve Formation)



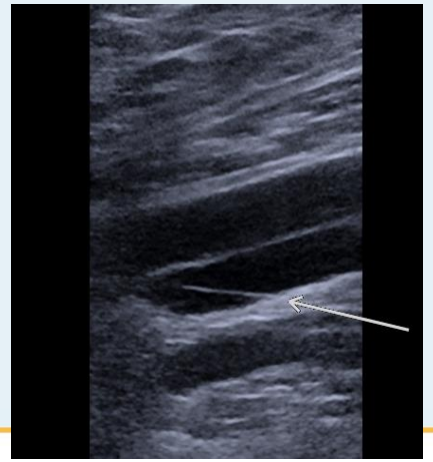
16 Fr Retrograde access,1-3 autogenous valve pockets/stations with no implant in fem & pop vein

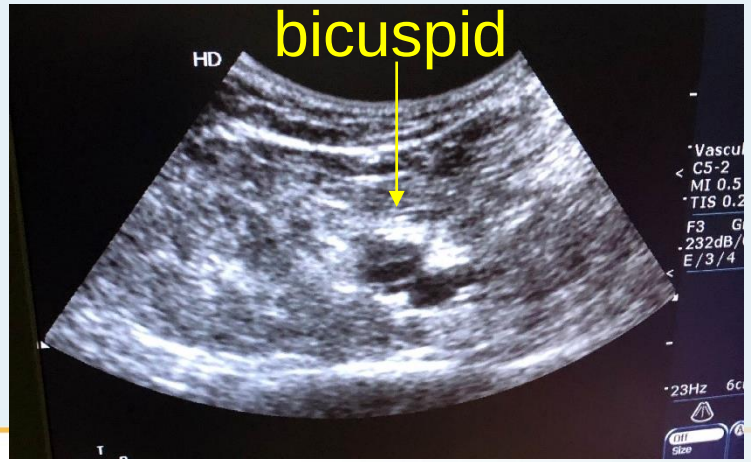


Cadaveric Monocuspid



Monocuspid & Bicuspid EVF Valves





W. Marston, UNC Chapel Hill, NC

R. Varcoe, Sydney, Australia (Tbilisi, RoG)

Summary of Clinical Experience

- n=36 cases, F/U 30d - > 2yrs, 3rd Gen catheter config w/ongoing improvement in procedure and peri-op valve formation, quality

- Favorable safety w/single asymptomatic DVT (<3%) @ discharge
  - Recanalized by 30 day f/u w/out intervention or change to meds, post-Op mgt
  - Few AE/complications, typical interventional & co-morbidity types
  - Very few adverse late issues to report

- Favorable clin improvement in VCSS as well as pain reduction via VAS

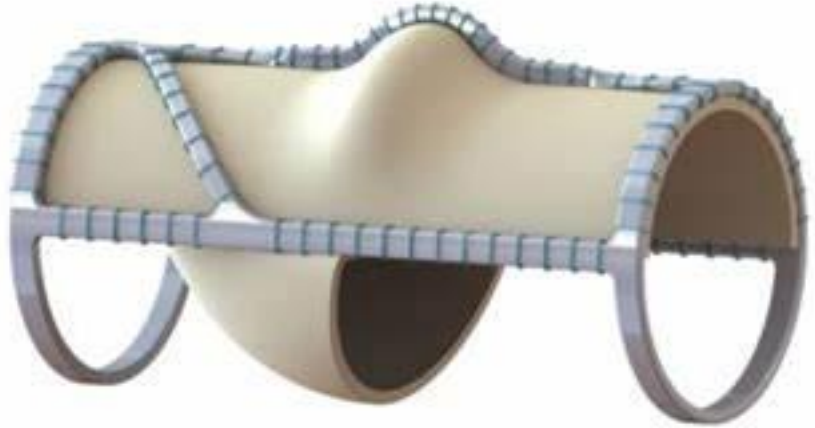
- First bicuspid valves (n= 11 pats) by 5 physicians, FDA recently authorized use in US EFS

- US EFS IDE completed n= 13 of 20 cases w/92% technical success rate, *Rec'd Breakthrough Device Designation, use of Bicuspids in EFS Dec 21*

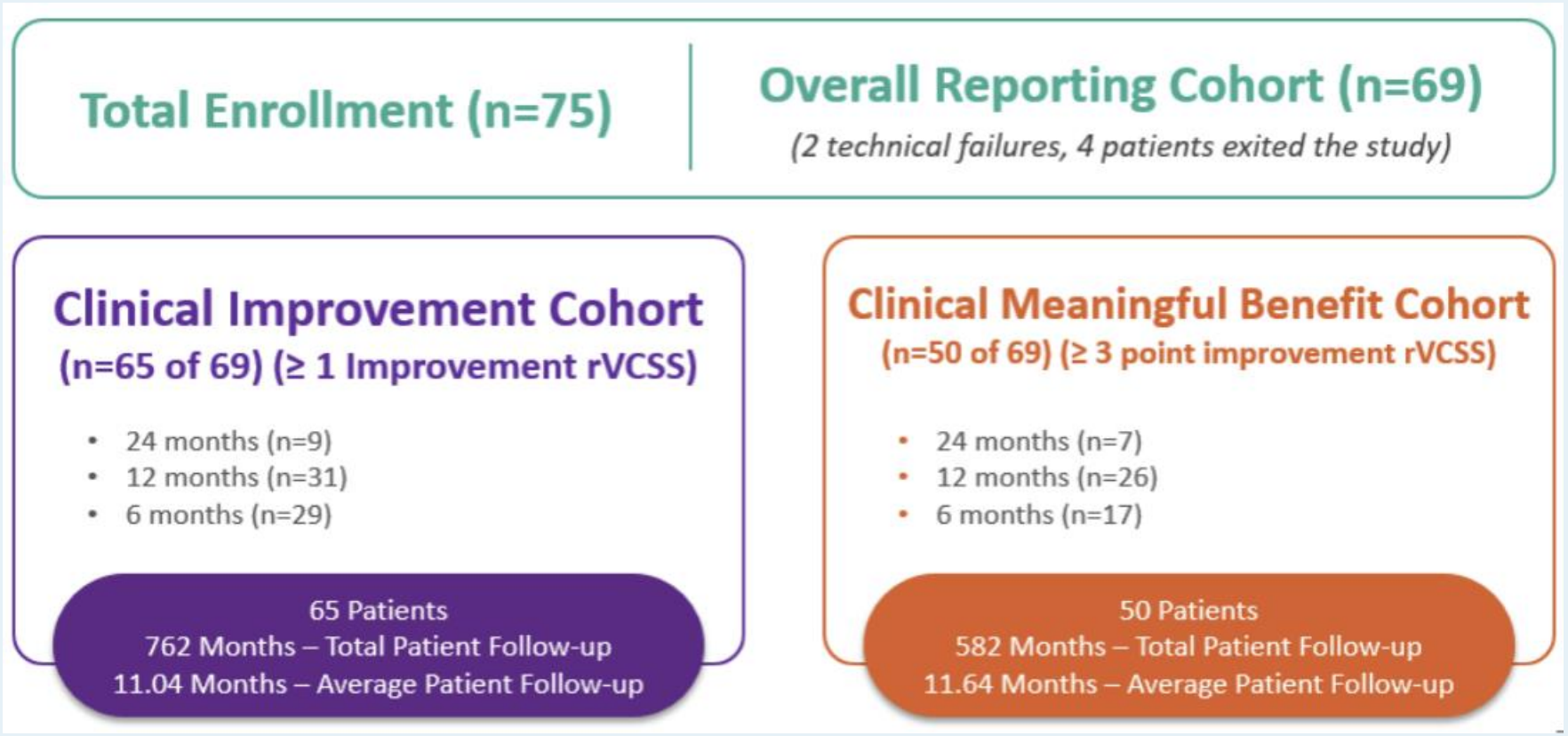
- *Gained experience re; procedure improvement/techniques, post-op valve imaging, hemodynamics, training, patient selection*

enVVeno

- Venous Valve Implantation
- FDA granted IDE approval to assess the safety and efficacy of the VenoValve for the treatment of patients with deep venous valvular insufficiency
- Prospective, non-blinded, single-arm, multi-center study
- 20 U.S. investigational sites
- 75 patient study
- CEAP Score: C4b – C6 patients



SAAVE Trial Outcomes



Conclusions

- We can do better in the prevention and treatment of PTS
- New Technology will allow more efficient thrombectomy and lower rates of PTS
- Newer Stents will allow for the treatment of IVC obstruction rather than just iliac obstruction
- The addition of anti-inflammatory agents is a promising technology to prevent early venous inflammation and reduce the rates of PTS
- Treatments for Deep Venous Reflux continue to evolve

Thank You

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