Venous Disease:
The missing link
an update

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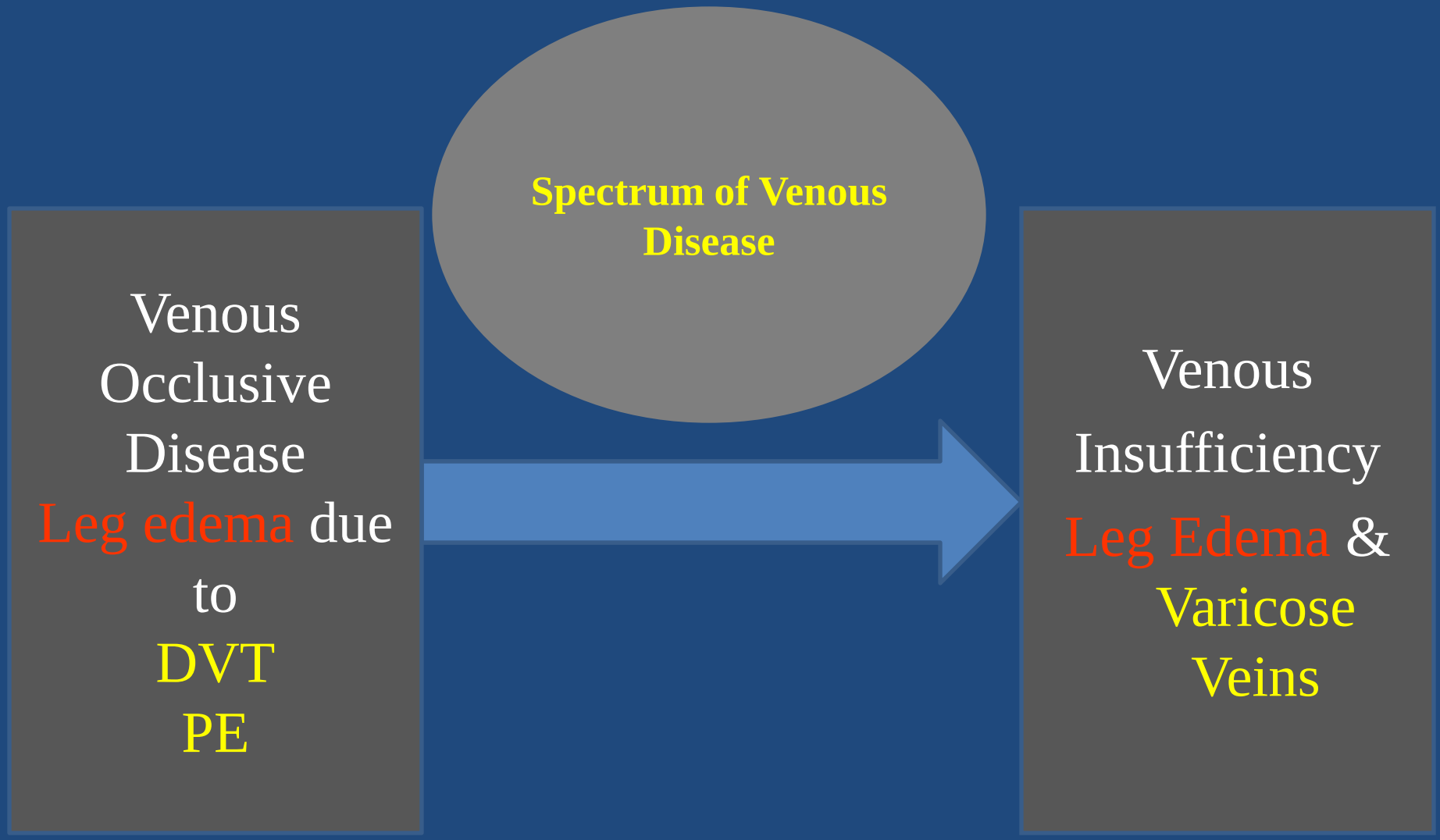
CVI: THE MISSING LINK

- Remember the triad of CV System:
- The heart
- The arteries
- The veins

- How can we focus so much on the heart and the arteries and so little on the veins


Spectrum of Venous Disease
Venous Occlusive Disease
Leg edema due to
DVT
PE
Venous Insufficiency
Leg Edema &
Varicose Veins

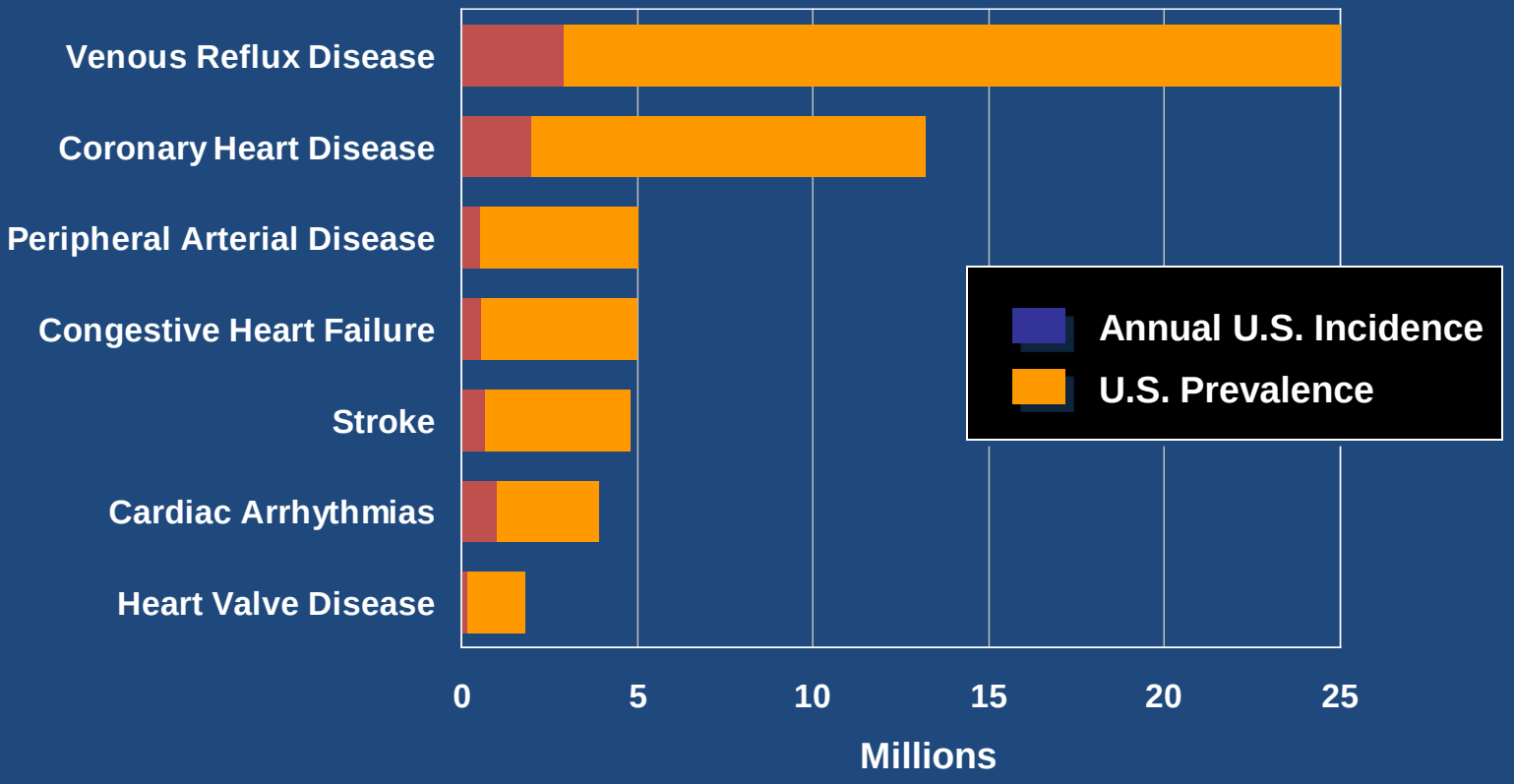
25 Million people suffer from venous reflux disease, the underlying cause for most varicose veins




Images courtesy of Paul McNeill, MD and Rajabrata Sarkar, MD

Prevalence and Etiology of Venous Insufficiency

Venous reflux disease is 2x more prevalent than coronary heart disease (CHD) and 5x more prevalent than peripheral arterial disease (PAD)[1]



Prevalence and Etiology of Venous Insufficiency

Of the estimated 25 million people with symptomatic superficial venous reflux[1] :

- Only 1.7 million seek treatment annually[2]
- Over 23 million go untreated

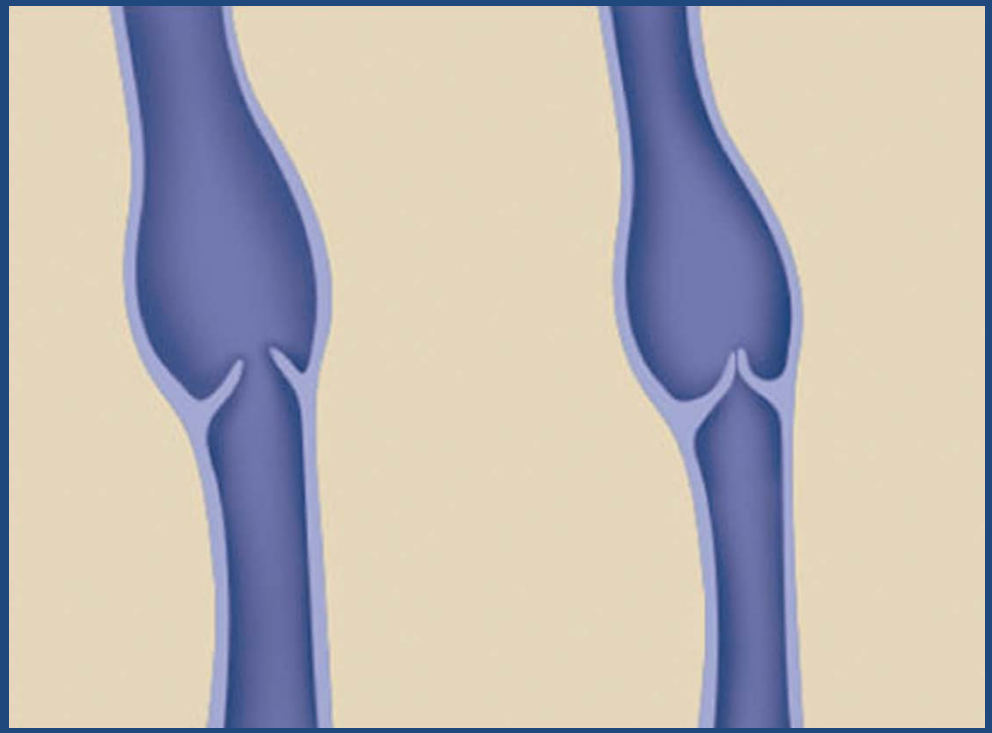
Prevalence by Age and Gender[3,4]

Age	Female	Male
20 - 29	8%	1%
40 - 49	41%	24%
60 - 69	72%	43%

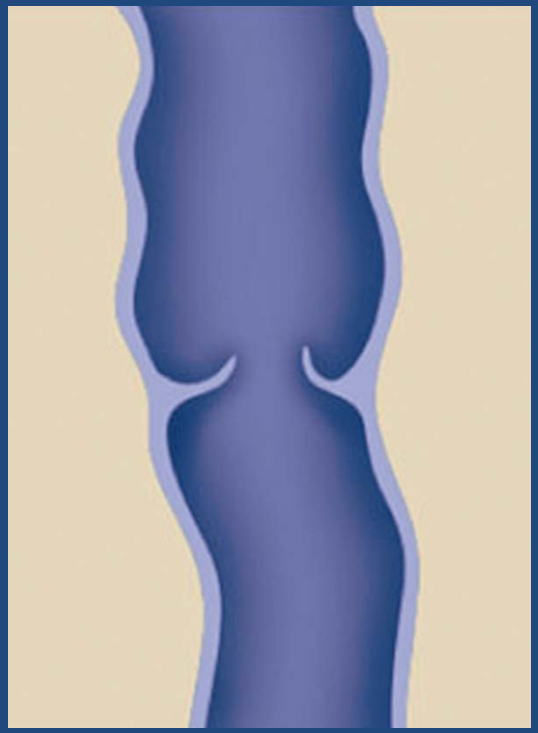
Venous Reflux Disease
What Is It?

- Venous valve becomes incompetent
  - Superficial vein >> deep vein
  - Increases weight of column of blood on adjacent, inferior valve, which is then more likely to fail
- Blood return from the deep venous system refluxes *down* the incompetent superficial veins ("ASD of the leg")
- Such venous hypercirculation may lead to *deep* venous valve failure
- Upright venous pressure at the ankle ultimately increases due to uninterrupted, unsupported column of blood and may exceed 80 mmHg

Vein Valve Failure

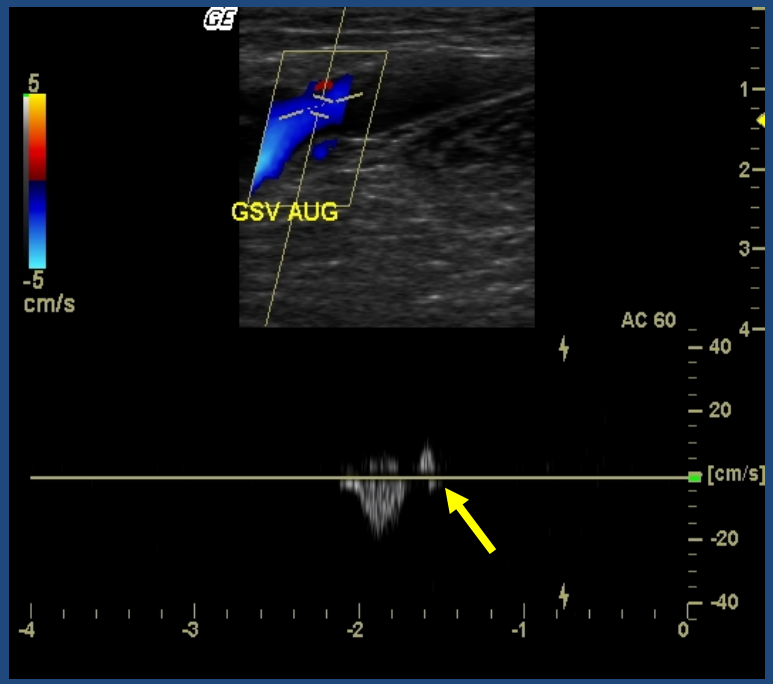


Normal vein: valve open and closed

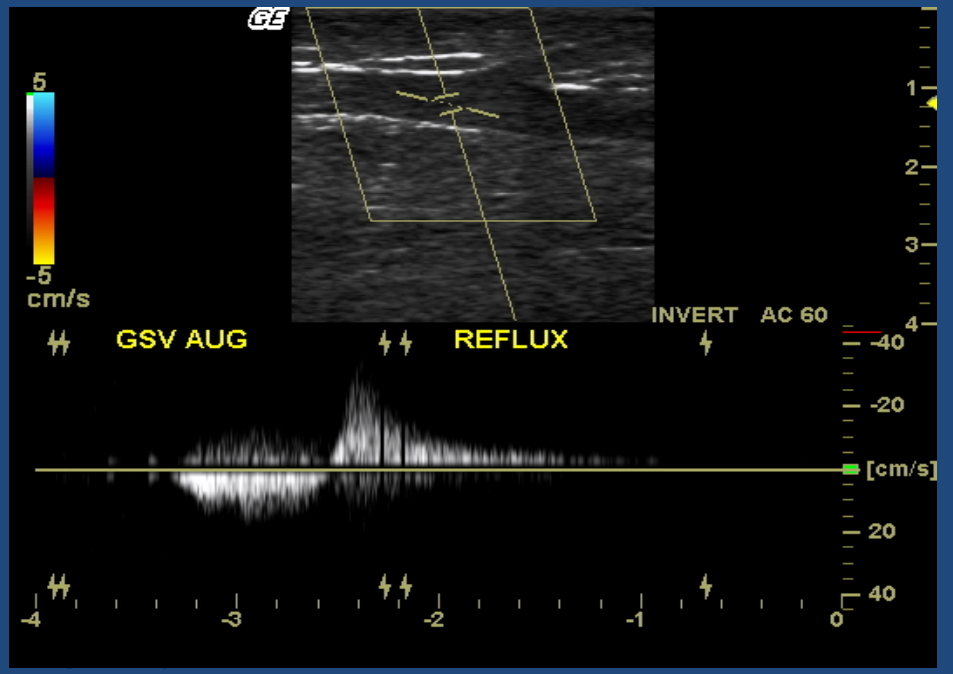


Dilated vein with non-functioning valve

Superficial System Exam:
Great Saphenous Vein



Normal valve closure time of <0.5 sec



Reflux of approximately 1.5 seconds

Important Facts about Venous Insufficiency!!

- With advancing age, especially with females, the prevalence of venous disease grows
- The typical female patient is in her 40's and has had multiple pregnancies
- It is estimated that in America, 72% of women and 42% of men will experience varicose veins by the time they reach their 60s (prevalence is highly correlated to age and gender)
- (Barron HC, Ross BA. Varicose Veins: A guide to prevention and treatment. NY, NY: Facts on File, Inc. [An Infobase Holdings Company]; 1995;vii

Radiofrequency Ablation Procedure Video

Vein Access

Vein access achieved percutaneously or through small cutdown

- An introducer sheath is placed in vein

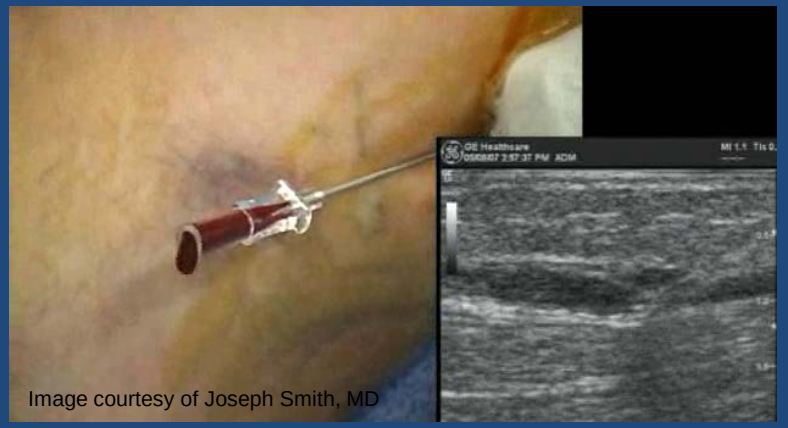


Image courtesy of Joseph Smith, MD

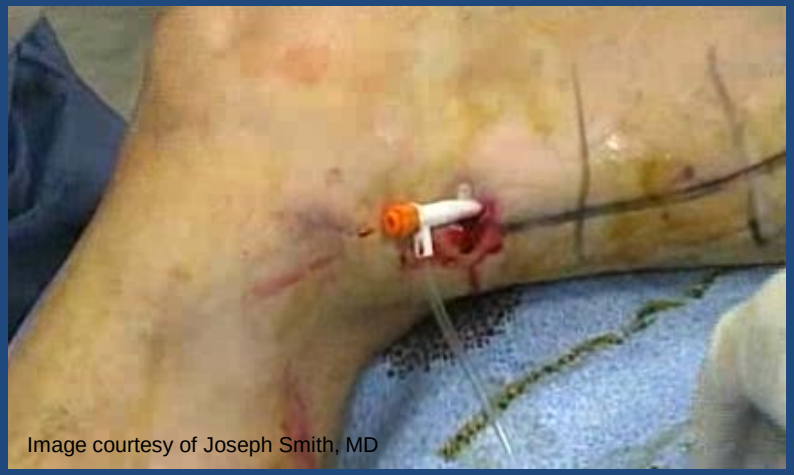


Image courtesy of Joseph Smith, MD

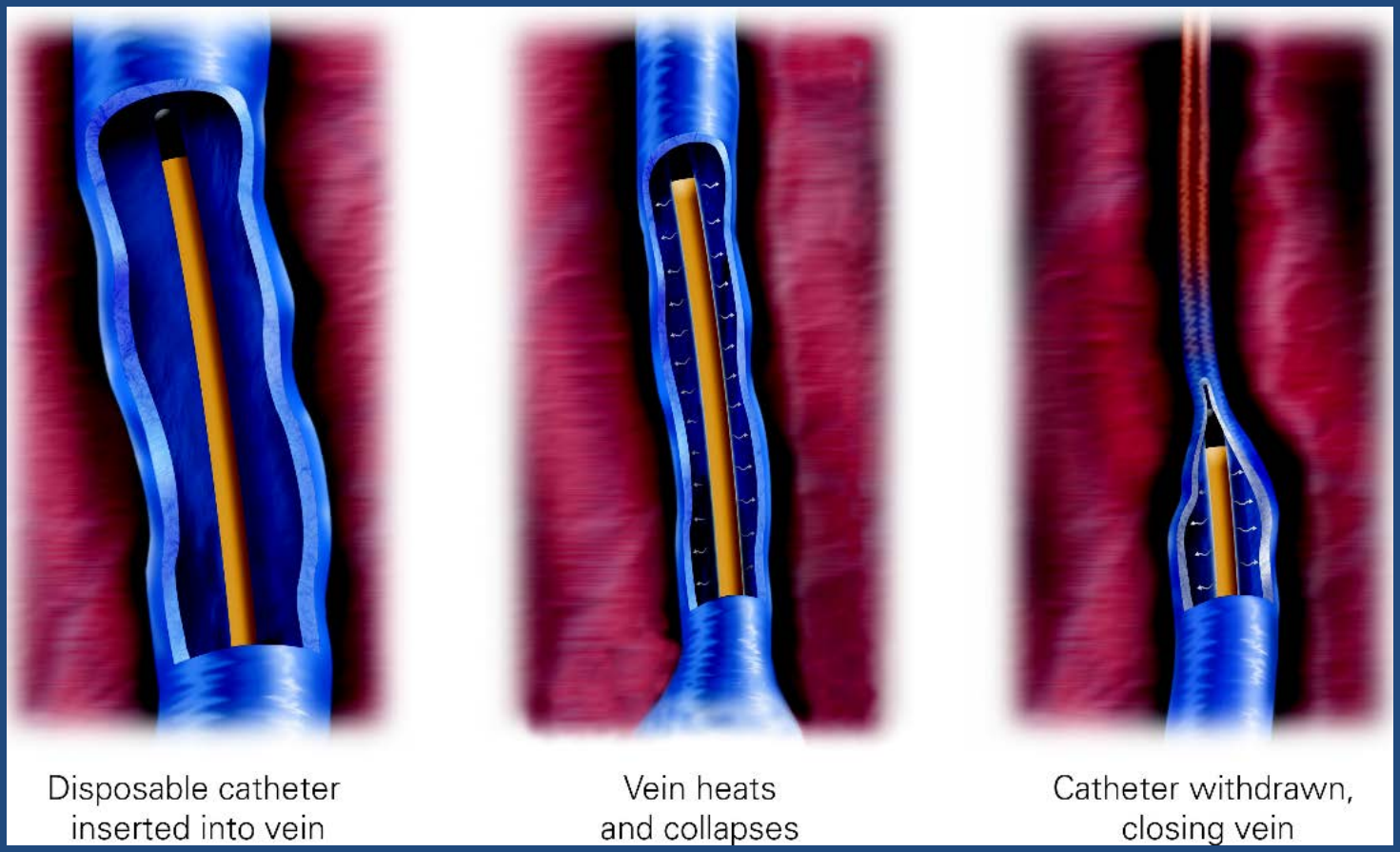
Tip Position Verification

- Catheter tip is positioned 2.0cm distal to SFJ under ultrasound guidance

Closure*FAST* System

- 7F with a 7cm heating coil
  - 7cm vein length treated at once
  - 6.5 cm index pullback between treatments
- Temperature controlled energy delivery
- Power on/off switch on handle
- 0.025” guidewire compatible
- FDA approved 3/99
- Bipolar electrode system heats vein wall to desired temperature using RF energy

VNUS Closure® Procedure using the ClosureFAST™ Catheter



Madyoon Experience

- 489 limbs were treated in 287 patients with CVI
- All patients were symptomatic (Edema, Pain, Leg Heaviness, Varicose Veins) & had reflux disease of GSV, SSV, and/or AAV
- RF ablation was used in majority (8 pts had Laser)
- Procedural Primary success rate 98%
- Procedural Secondary success rate 100%
- Procedural long term success rate 99%
  - Only 3 patients had non-closure of the vein

Madyoon Experience

- Complications
  - Thrombus — 15 procedures (3%)
  - Pain after procedure along the length of the ablated vein — 18 procedures (3%)
  - Ecchymosis — 26 procedures (5%)
  - Nerve damage — 10 procedures (2%)

Madyoon Experience

- Resolution of edema, pain leg heaviness and varicose veins — 275 (96%)
- Decrease in weight, BP or number of diuretics and other BP medications — 89 (31%)
- Improvement in the symptoms of SOB, Fatigue Decreased Exercise Tolerance — 80 (28%)

The Hypothesis

- These observations have lead to the hypothesis that CVI may have significant systemic effects and may cause Neuro-hormonal activation by reducing the effective circulating volume, similar to what happens in patients with Heart Failure!

- The subsequent increase in renin/angiotensin/aldosterone levels and the sympathetic tone, results in *excessive salt and water retention* and exerts deleterious effects on cardiovascular system, causing or worsening endothelial cell dysfunction, CHF and HTN!

The new pilot clinical trial

- Twenty pts with CVI due to GSV reflux, and leg edema, with and without CHF will be evaluated for Neurohormonal activation and excess body fluids by measurement of:
  - Rennin, angiotensin, aldosterone, serum K, BNP, Cathecolamines, and Cardiac MRI (RV and/or LV dysfunction)
  - weight, BP, change in medications, and quality of life

- Before and 4 weeks after treatment CVI

Future trials

- The incidence of severe CVI in patients with CHF and leg edema
- Randomized trial of interventional therapy vs conventional therapy (compression stockings, diuretics….) on neurohormonal activation and clinical outcomes in patients with CHF or HTN who have leg edema and CVI
- More ideas are welcome

DVT - "A National Crisis…"

- U.S. Surgeon General, 2008

- >600,000 Americans are diagnosed with DVT annually[1]
- 300,000 will develop Post Thrombotic Syndrome (PTS)[2,4]
- 120,000 will suffer recurrent VTE (DVT/PE)[3]
- VTE is the leading cause of preventable hospital death[5] (DVT and PE)
- DVT is the third most common CV Disease[4]
- U.S. spends $2.4B to Treat DVT annually[2]

1. Heit, JA. Venous Thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 2005; 3:1611-17
2. Sharafuddin, M. et al. Endovascular Management of Venous Thrombotic and Occlusive Diseases of the Lower Extremities. J Vasc Interv Radiol 2003; 14:405-423
3. Spencer FA et al. Patient Outcomes After Deep Vein Thrombosis and Pulmonary Embolism: The Worcester Venous Thromboembolism Study. Arch Intern Med. 2008; 168: 425-430
4. Arko F et al. Aggressive Percutaneous Mechanical Thrombectomy of Deep Vein Thrombosis. Arch Surg. 2007;142:513-519
5. National Quality Forum."National Voluntary Consensus Standards for Prevention and Care of Venous Thromboembolism: Policy, Preferred Practices, and Initial Performance Measures." 2008

2008: Paradigm Shift in DVT Treatment

National Quality Forum & Joint Commission

- Publishes a consensus statement requiring protocols for DVT prophylaxis and treatment
  www.qualityforum.org/publications/reports/vte.asp

American College of Chest Physicians

- Releases updated clinical practice guidelines that suggest the use of pharmacomechanical thrombolysis for acute proximal DVT

Chest 2008; 133; 454-545 DOI10.1378/chest.08-0658

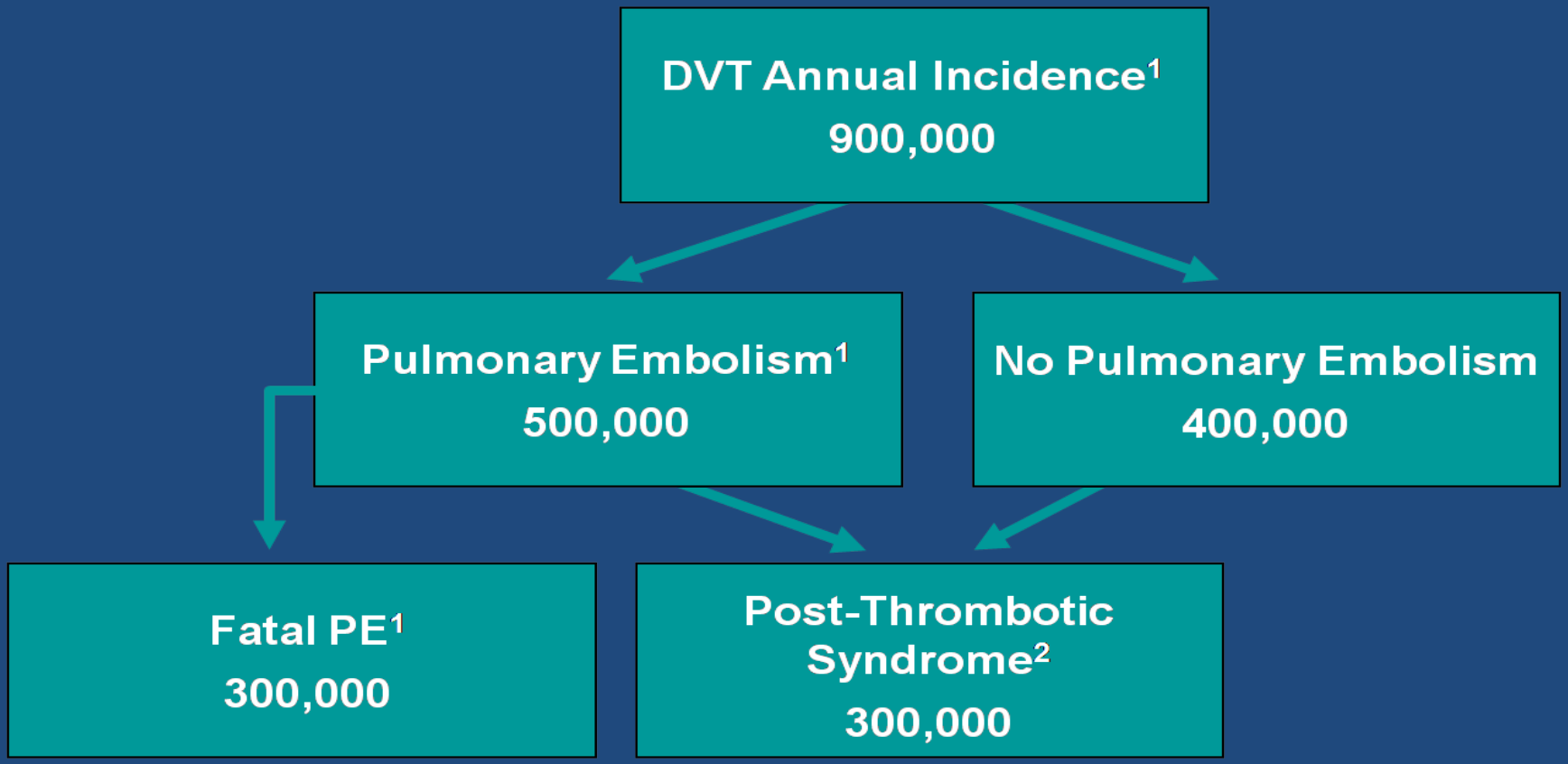
Office of the Surgeon General

- Releases 7th Call to Action in 11 years focusing on DVT as a national health issue
  www.surgeongeneral.gov/topics/deepvein/

American Journal of Medicine

- Dedicates entire supplement to prophylaxis and treatment of DVT with focus on aggressive removal of select DVT's and institutional need to develop DVT protocol
  AJM Volume 121, Issue 11, Supplement 1 (November 2008)

Annual Incidence of VTE (# of Patients)



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Prospective Studies of the Frequency of PTS after Symptomatic DVT

	DVT Type	FU (years)	percent PTS
Strandess et al.	Any	2	67%
Kakkar & Lawrence	Any	2	84%
Monreal et al	First	3	56%
Johnson et al	Any	3	41%
Prandoni et al	First	8	29%
Brandjes et al	First (proximal)	6	50.7%
Franzeck et al	Any	12	36%
AbuRahma et al	First (proximal)	5	36%
Masuda et al	Distal	3	57%
Meissner et al	First	4.5	73%
Saarinen	Any	2	73%
Ginsberg	First (proximal)	1	27%
Haenen	Any	2	77%

Kahn, S. and Ginsberg. *The Relationship between Deep Venous Thrombosis and The Postthrombotic Syndrome*. Arch Internal Medicine. Volume 164, January 12, 2004.

VTE in Hospitalized Patients Not Just a Surgical Problem

50%-70% of symptomatic VTEs occur in nonsurgical patients

70%-80% of fatal PEs occur in nonsurgical patients

DVT was detected by ultrasound in 33% of medical patients in the ICU during an 8-month screening study

PE: most preventable cause of hospital death and the number one strategy to improve patient safety in hospitals

1. Geerts WH, et al. Chest . 2008;133:381S-453S.
2. Hirsch DR, et al. JAMA . 1995;274:335-337.

Anticoagulation alone…

…does prevent clot propagation.

…does reduce risk of pulmonary embolism.

…does not resolve clot.

…does not prevent valvular damage.

…does not prevent venous hypertension.

…does not rapidly resolve symptoms.

…does not prevent PTS.

Important Fact on Proximal DVT

21% of *adequately anti-coagulated* patients develop PE

Up to 50% of patients on anticoagulation develop PTS in 3-5 years

Estimated cost of VTE is $1.5 Billion

(Plate G, Ohlin P, Eklof B. Pulmonary embolism in the acute ileofemoral venous thrombosis. Br J Surg 1985;72:912–915.)

Anticoagulation alone…

…is not enough.

What if?

What if a DVT patient …

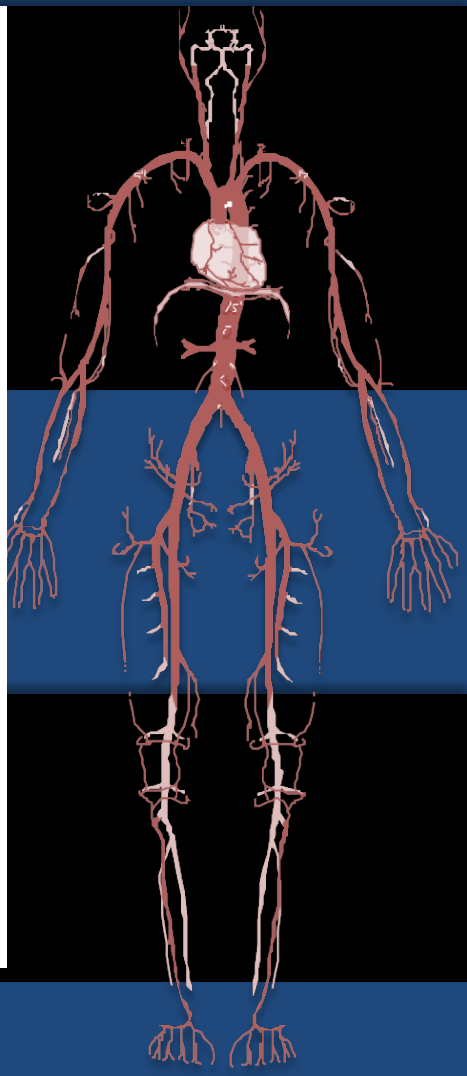
- …could be treated in less than 2 hours and be home in less than 2 days?
- …had reduced chances for developing PTS?

What if…

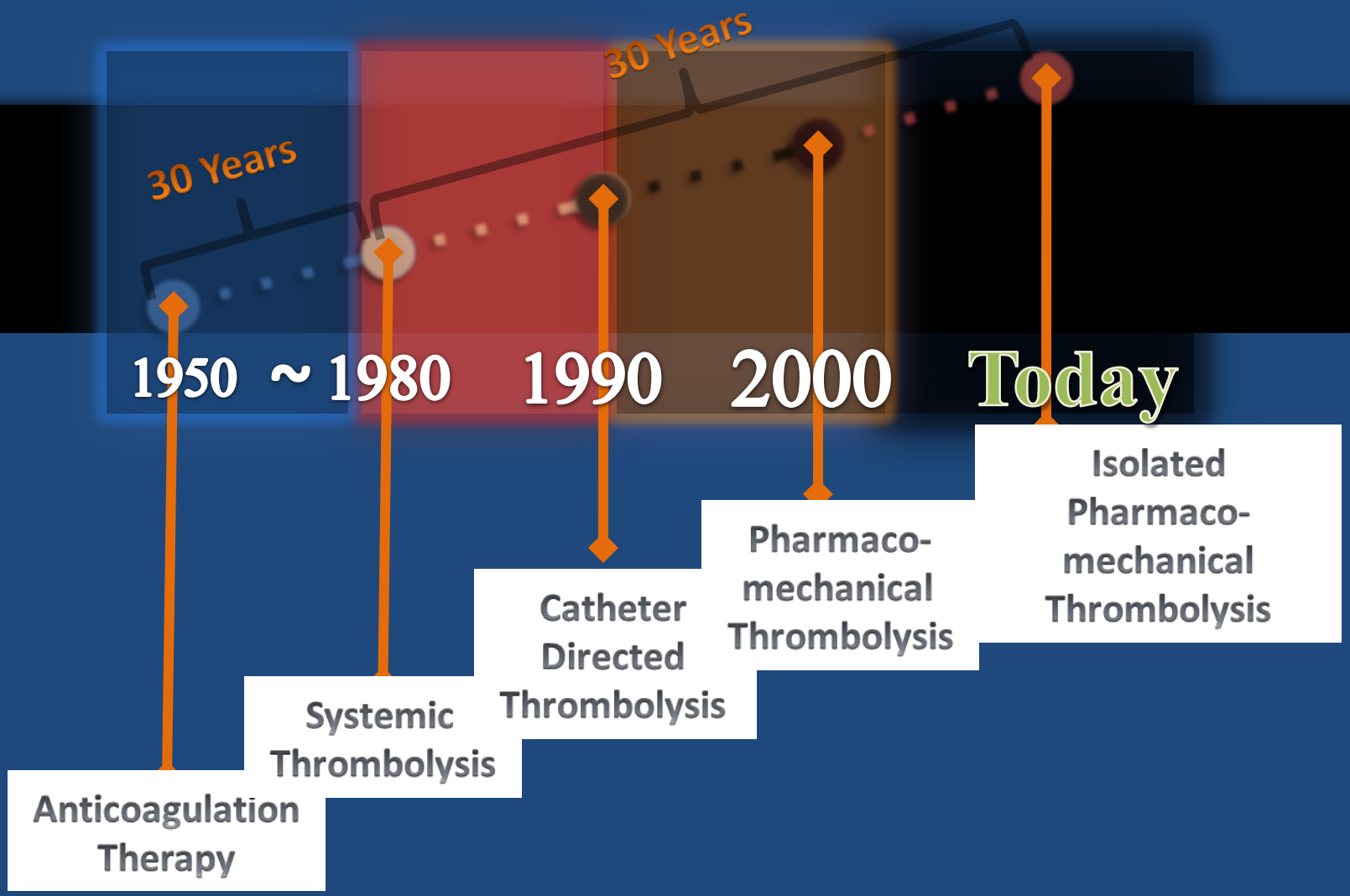
- …the largest DVT clinical registry demonstrated a safe and effective treatment?

Would you…

- …consider changing your DVT treatment plan?



The Evolution of DVT Treatment



Isolation + Pharmacomechanical Thrombolysis (Isolated PMT)

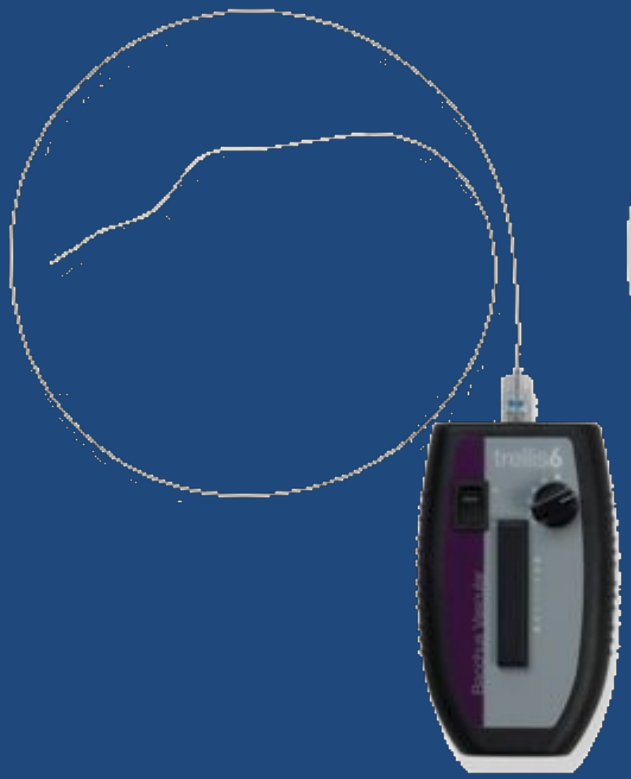
Pharmacomechanical Thrombolysis Treatments (PMT)

- Thrombolytic infusion with mechanical energy
- Dissolves and macerates thrombus
- Reduces the thrombolytic dose & time

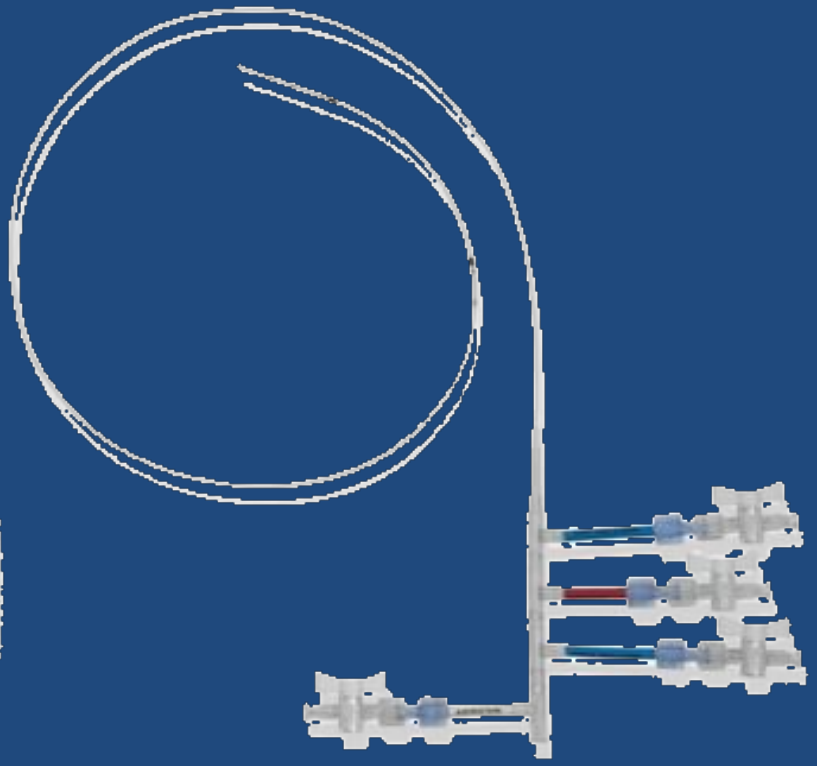
Isolated Pharmacomechanical Thrombolysis Treatments (Isolated PMT)

- Thrombus isolated between occluding balloons
- Lytic isolated between occluding balloons
- Reduction in thrombolytic dosing
- Aspiration of thrombus and lytic
- Single setting thrombus removal
- No reported major bleeding
- Reduces/eliminates ICU time

The Trellis™Peripheral Infusion System



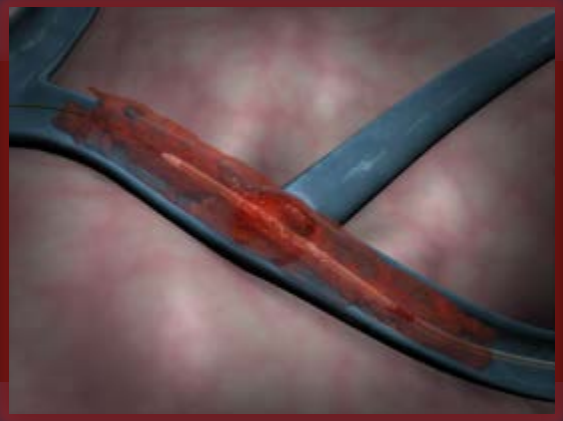
Trellis Oscillation Drive Unit (ODU) and Dispersion Wire



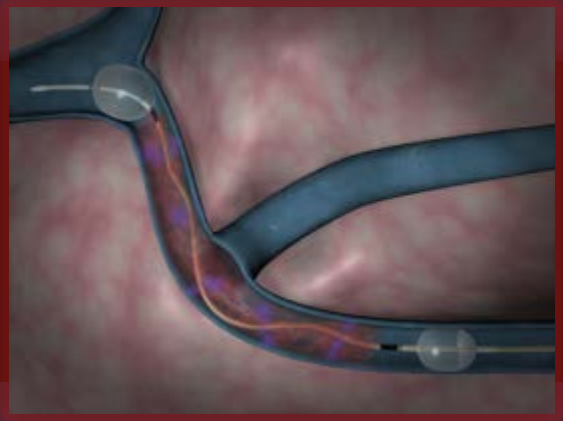
Trellis System Catheter

Isolated Pharmacomechanical Thrombolysis

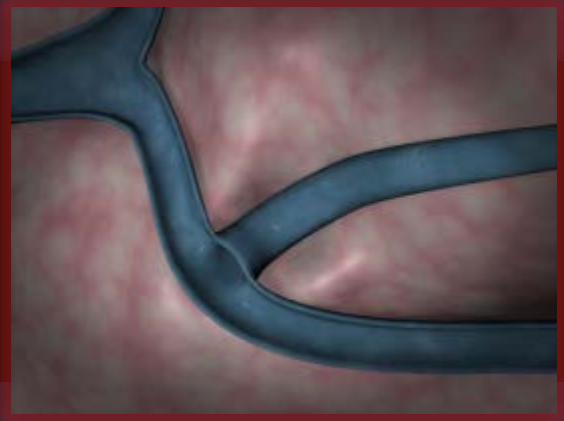
How It Works



Catheter delivered over guidewire



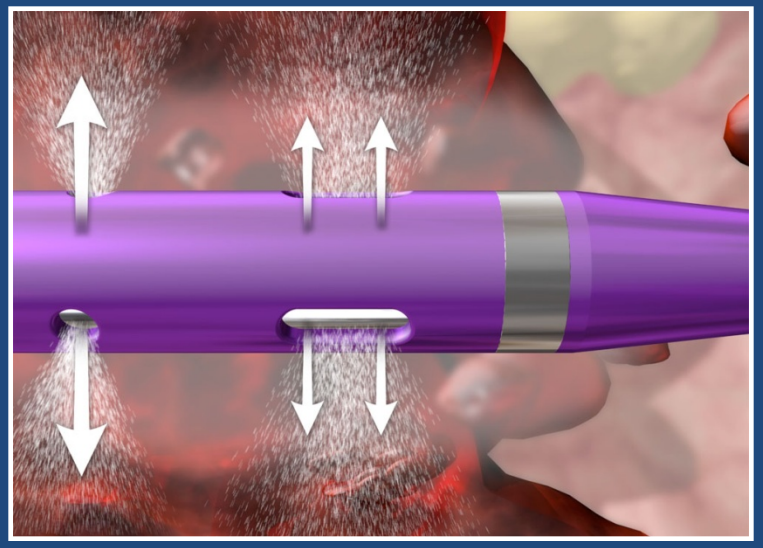
Thrombus isolated & targeted delivery of thrombolytic drug



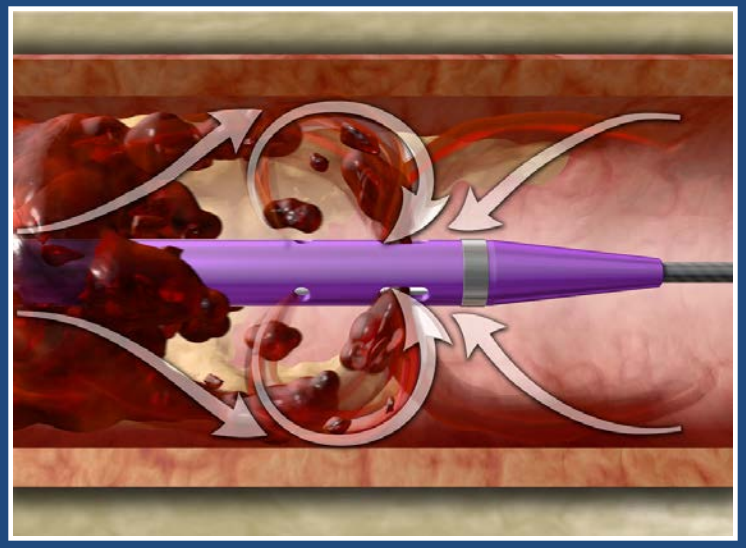
Single-setting treatment in 83% of cases*

Dual Functionality

Single-Catheter Option for Combination Therapy



Power Pulse® Delivery INFUSION of physician-specified fluid (PSF)



Thrombus REMOVAL

Limitation of Anticoagulation

- Effective in preventing thrombus propagation and PE
- Does not prevent PTS
- Often occurs years after the originial thrombotic event

Catheter directed therapy

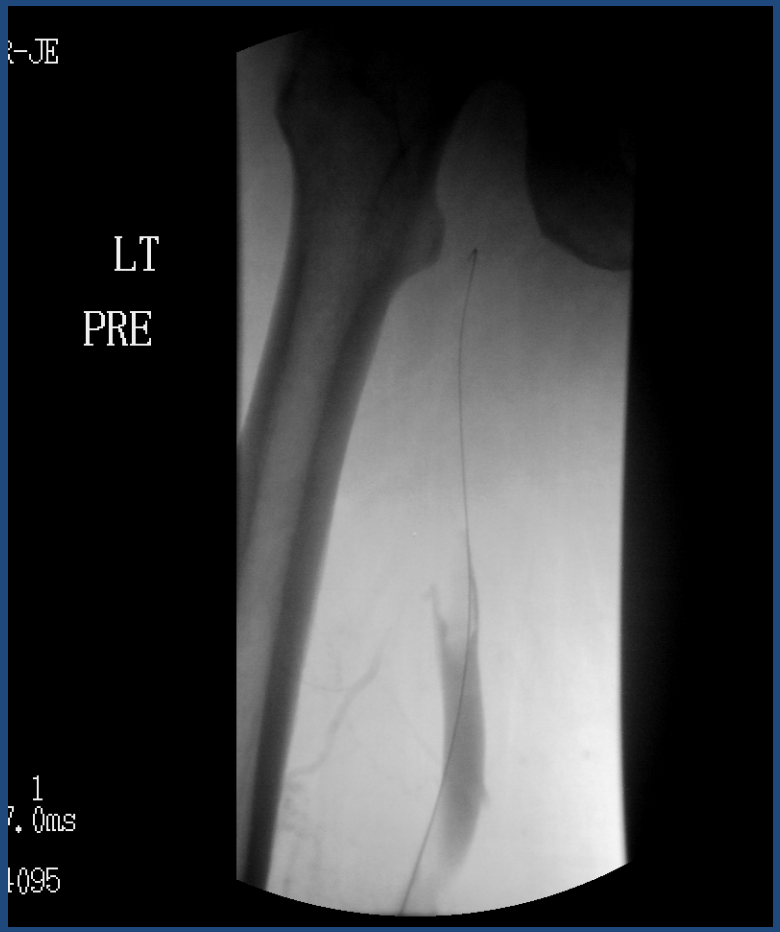
- Rapid reduction in thrombus burden
- Preservation of venous valve function
- Prevention of PTS
- Catheter directed thrombolysis registry
  - 83% of patients had improved quality of life compared to historical cohort of patients treated with anticoagulation

Acute on chronic DVT

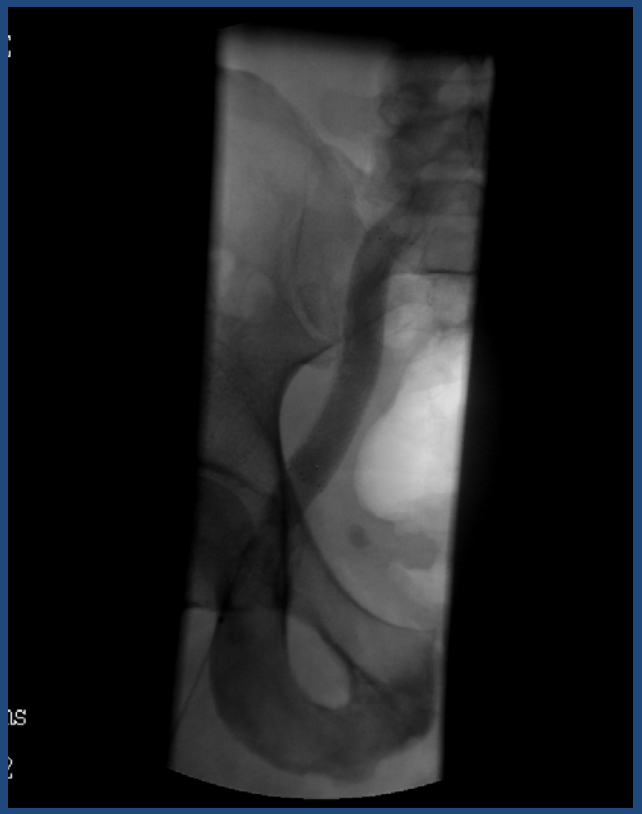
- Lower extremity DVT with pain and swelling
- Patient states symptoms have been worsening over 3 months

After thrombolysis

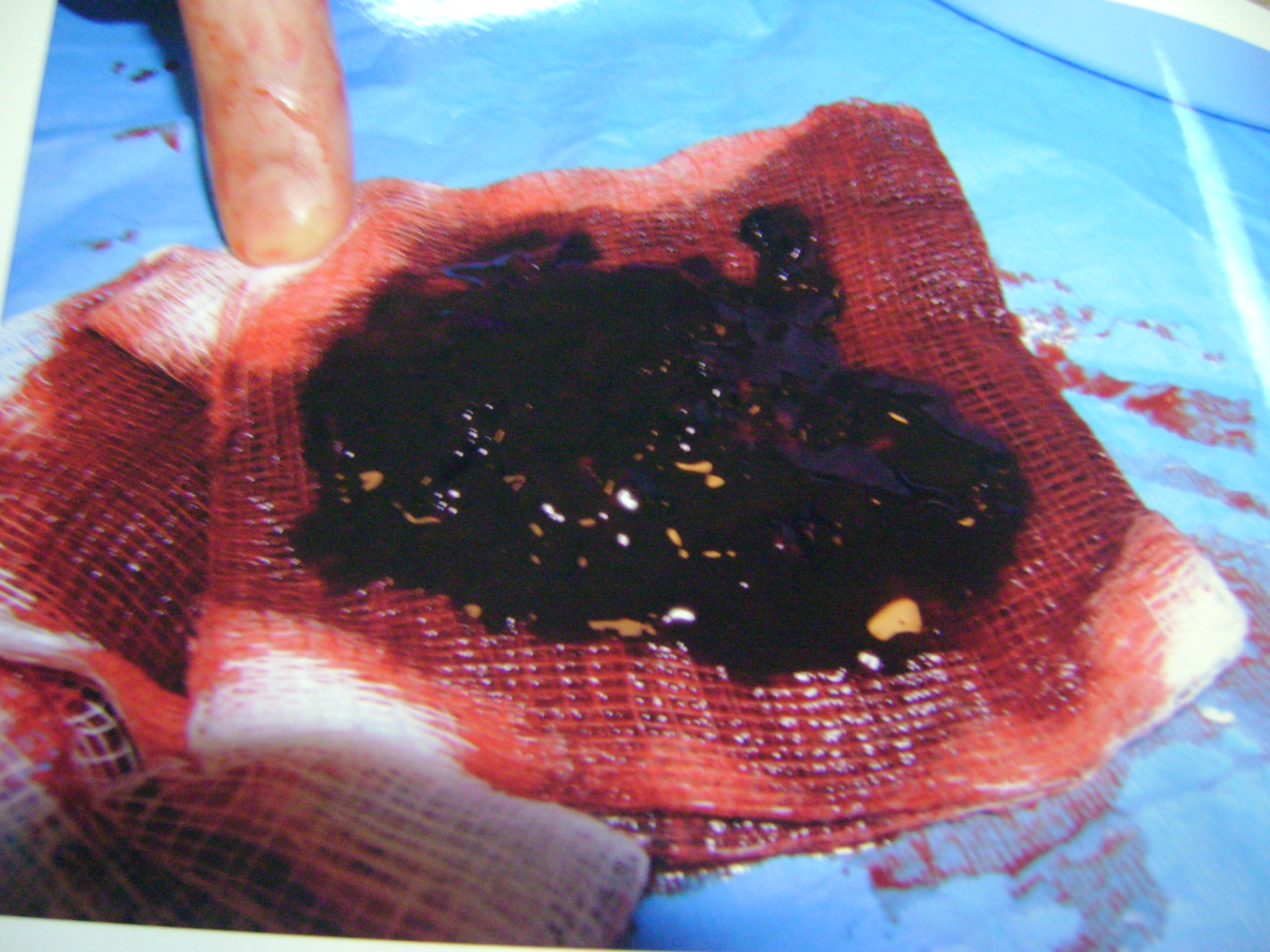
45 year old with extensive leg swelling secondary to DVT

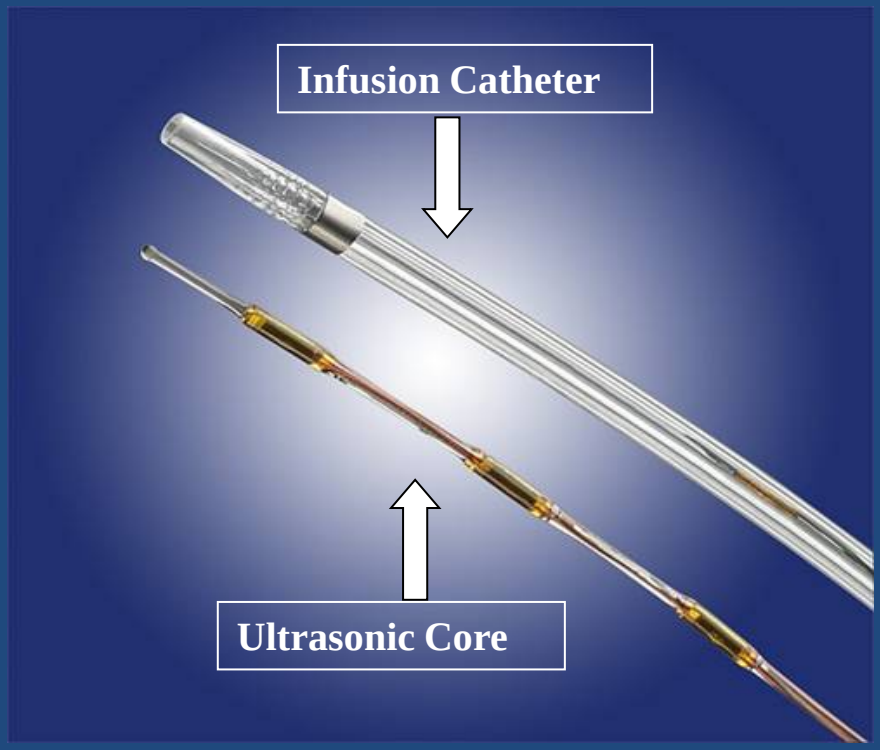


s/p angiojet treatment of DVT. Stenting of persistent narrowing of iliac vein

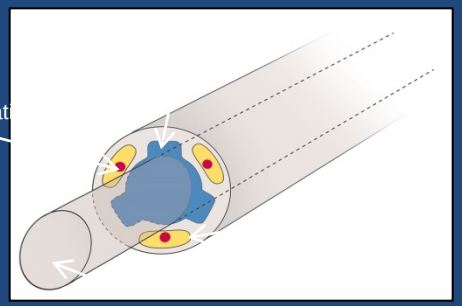



PHILIPS





Therapy Optimizat



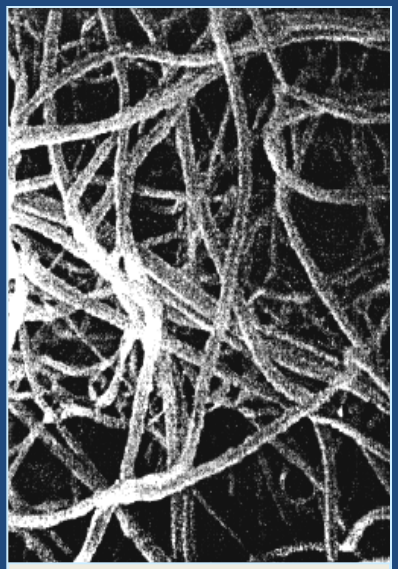
Features

- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones

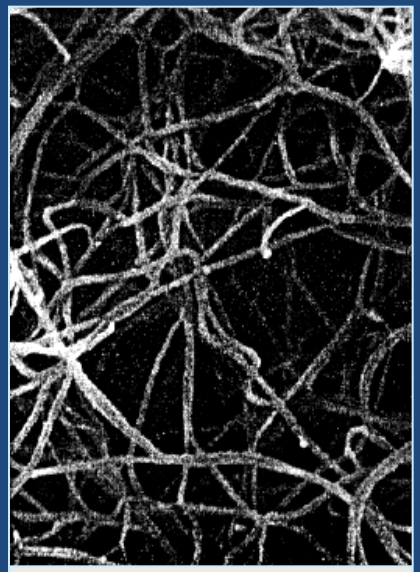
Mechanism of action

Fibrin Separation

Non-cavitational ultrasound separates fibrin without fragmentation of emboli



Fibrin without Ultrasound

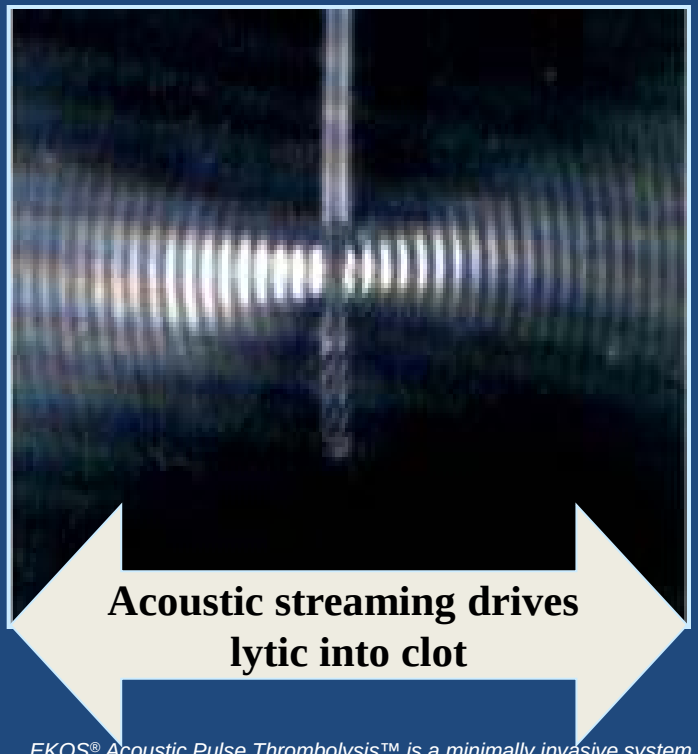


Fibrin With Ultrasound

Braatan et al. Thrmob Haemost 1997;78:1063-8.
Francis et al. Ultrasound in Medicine and Biology, 1995;21(5):419-24.
Soltani et al. Physics in Medicine and Biology, 2008; 53:6837-47.

Active Drug Delivery

Drug is actively driven into clot by "Acoustic Streaming"

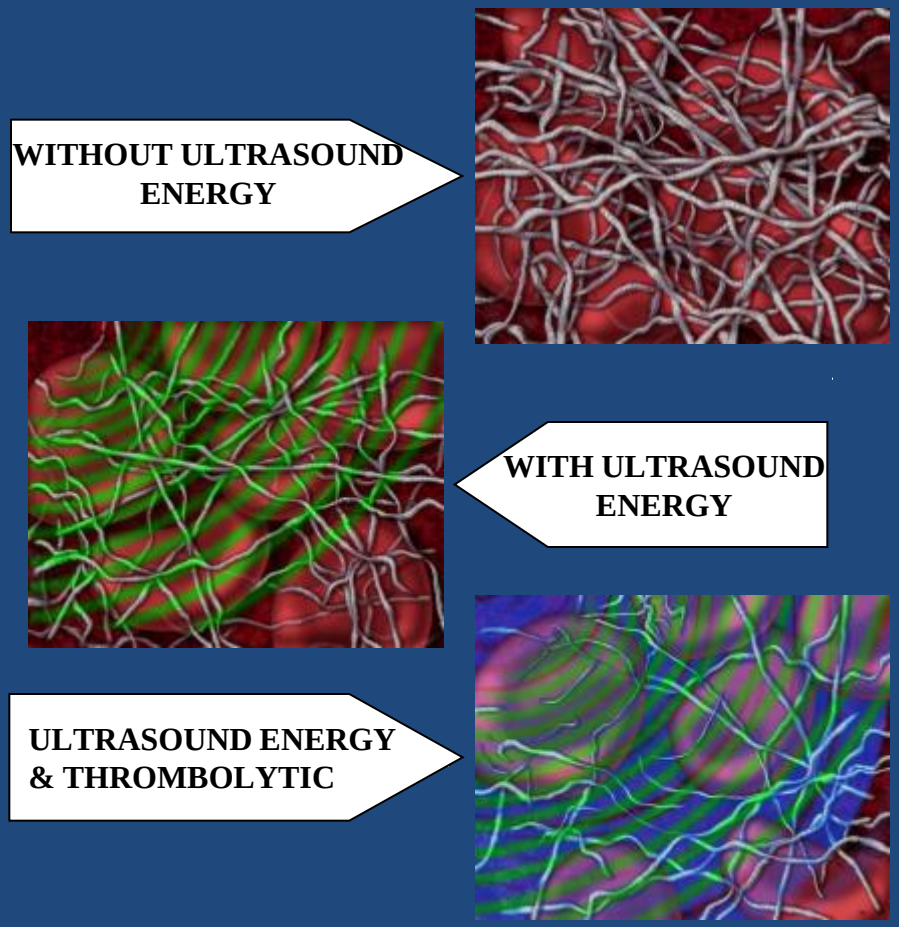


EKOS® Acoustic Pulse Thrombolysis™ is a minimally invasive system for dissolving thrombus.

Mechanism of action

How ultrasonic energy unlocks the clot

- Ultrasonic energy causes fibrin strands to thin, exposing plasminogen receptor sites and fibrin strands to loosen
- Thrombus permeability and lytic penetration are dramatically increased
- Ultrasound pressure waves force lytic agent deep into the clot and keep it there



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76 y/o male s/p trans-septal mitral valve-in-valve implantation

Patient presenting 3 days post-procedure with right femoral DVT

- Right femoral venous access site closed with Perclose suture
- Patient referred for catheter based therapy (EKOS), due to severe pain and swelling.
- The significant thrombus burden, increased the risk of PE in this patient with severe COPD (on home oxygen) and severe pulmonary hypertension (would not tolerate another insult to her poor respiratory reserve function)

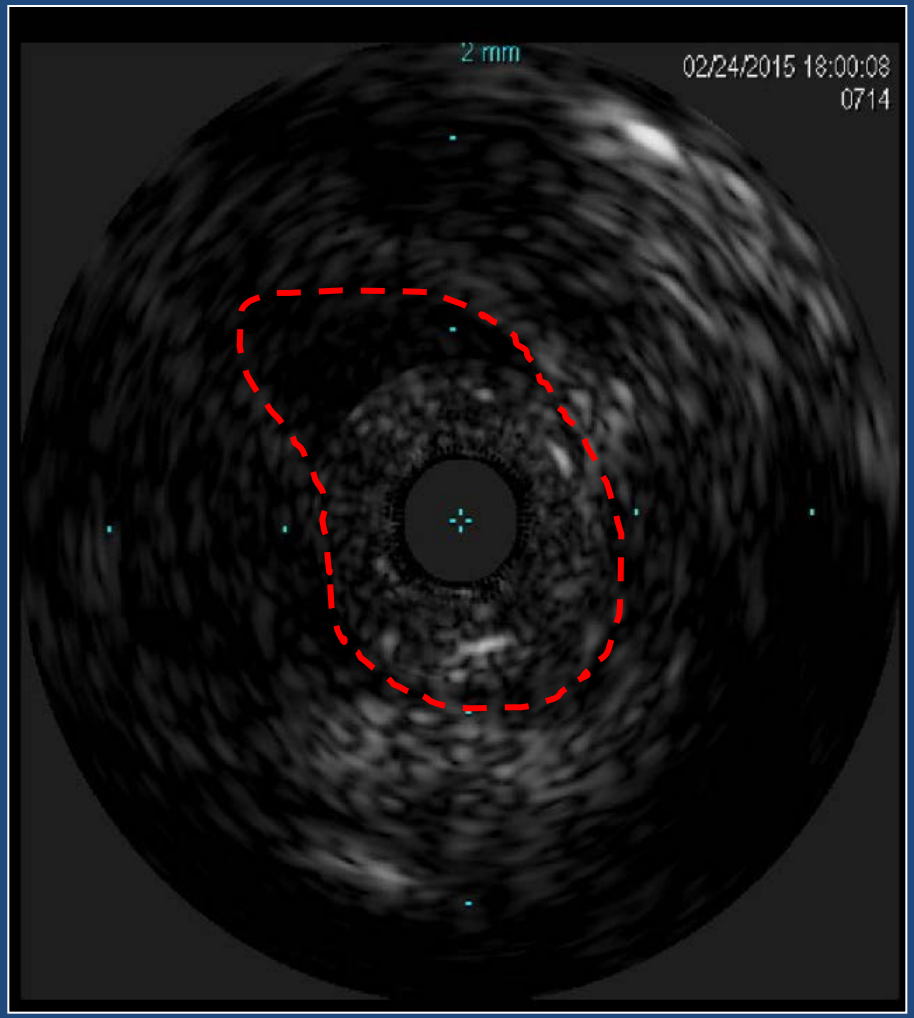
Significant thrombus in the right femoral venous system

EKOS Ultrasound catheter placed
Heparin and tPA infusion continued x 24 hours

Resolution of the high thrombus burden with patent flow from below the knee into the IVC

s/p 24 hours of heparin/tPA infusion

Right femoral venous IVUS showed significant stenosis at the site of Perclose suture



Balloon angioplasty of the right common femoral vein

Admiral Xtreme 10 x 40 x 130 balloon

Recoil stenosis after balloon angioplasty

Protege 14 x 60 self-expanding stent deployed, f/b post-dilation with EverCross 10 x 20 balloon

Patient doing well 5 days post-procedure

PE: A silent and fatal epidemic

– PE causes or contributes to 15% of all hospital deaths[1,2]

– More people die each year from PE than highway fatalities, breast cancer and AIDS combined[3]

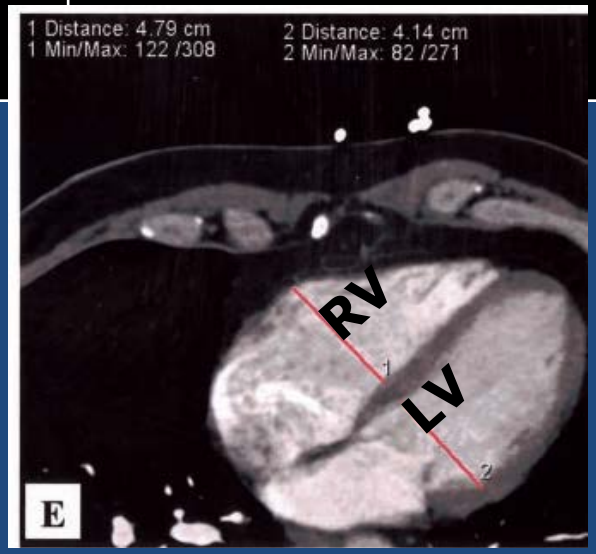
Cause of Death	# of deaths/yr
PE[4,5]	Up to 200,000
Highway fatalities[6]	42,116
Breast Cancer[7]	40,200
AIDS[8]	14,499

1. Kasper et al. J Am Coll Cardiol. 1997;30:1165-1171
2. According to http://www.sirweb.org/patients/deep-vein-thrombosis/
3. Goldhaber. Deep-vein thrombosis: Advancing awareness to protect patient lives. American Public Health Association White Paper. 2003.
4. Anderson et al. Arch Intern Med. 1991;151:933-938.
5. Silverstein et al. Arch Internal Med. 1998;158:585-593.
6. National Highway and Traffic Safety Association. Fatality Analysis Reporting System (FARS) Web-Based Encyclopedia. Accessed January 31, 2002.
7. American Cancer Society. Breast cancer facts and figures, 2001-2002. Accessed January 31, 2002.
8. Centers for Disease Control Report. HIV/AIDS Surveillance Report 2001. Volume 13, Number 2.

Patient risk stratification (per AHA Scientific Statement 2011[1])		
Massive PE	**Submassive PE**	**Minor/Nonmassive PE**
High risk	**Moderate/intermediate risk**	**Low risk**
– Sustained hypotension (systolic BP <90 mmHg for ≥15 min) – Inotropic support – Pulselessness – Persistent profound bradycardia (HR <40 bpm with signs or symptoms of shock)	– Systemically normotensive (systolic BP ≥90 mmHg) – **RV dysfunction** – Myocardial necrosis	– Systemically normotensive (systolic BP ≥90 mmHg) – No RV dysfunction – No myocardial necrosis

RV dysfunction

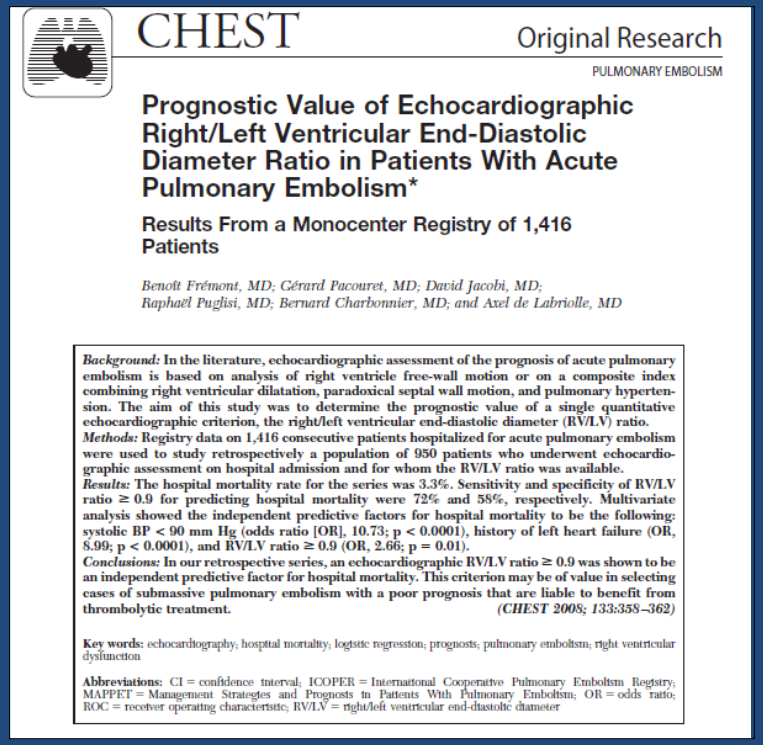
- RV/LV ratio > 0.9 or RV systolic dysfunction on echo
- RV/LV ratio > 0.9 on CT
- Elevation of BNP (>90 pg/mL)
- Elevation of NTpro-BNP (>500 pg/mL)
- ECG changes:
  - new complete or incomplete RBBB
  - anteroseptal ST elevation or depression
  - anteroseptal T-wave inversion



Jaff et al. Circulation 2011;123(16):1788-1830 Quiroz et. al. Circulation. 2004;109:2401-2404.

Adverse outcomes associated with RVD

Echocardiographic RV/LV ratio ≥ 0.9 shown to be independent predictive factor of hospital mortality



CHEST Original Research

PULMONARY EMBOLISM

Prognostic Value of Echocardiographic Right/Left Ventricular End-Diastolic Diameter Ratio in Patients With Acute Pulmonary Embolism*

Results From a Monocenter Registry of 1,416 Patients

Benoît Frémont, MD; Gérard Pacouret, MD; David Jacobi, MD; Raphaël Puglisi, MD; Bernard Charbonnier, MD; and Axel de Labriolle, MD

Background: **In the literature, echocardiographic assessment of the prognosis of acute pulmonary embolism is based on analysis of right ventricle free-wall motion or on a composite index combining right ventricular dilatation, paradoxical septal wall motion, and pulmonary hypertension. The aim of this study was to determine the prognostic value of a single quantitative echocardiographic criterion, the right/left ventricular end-diastolic diameter (RV/LV) ratio.**
Methods: **Registry data on 1,416 consecutive patients hospitalized for acute pulmonary embolism were used to study retrospectively a population of 950 patients who underwent echocardiographic assessment on hospital admission and for whom the RV/LV ratio was available.**
Results: **The hospital mortality rate for the series was 3.3%. Sensitivity and specificity of RV/LV ratio ≥ 0.9 for predicting hospital mortality were 72% and 58%, respectively. Multivariate analysis showed the independent predictive factors for hospital mortality to be the following: systolic BP < 90 mm Hg (odds ratio [OR], 10.73; p < 0.0001), history of left heart failure (OR, 8.99; p < 0.0001), and RV/LV ratio ≥ 0.9 (OR, 2.66; p = 0.01).**
Conclusions: **In our retrospective series, an echocardiographic RV/LV ratio ≥ 0.9 was shown to be an independent predictive factor for hospital mortality. This criterion may be of value in selecting cases of submassive pulmonary embolism with a poor prognosis that are liable to benefit from thrombolytic treatment.** ***(CHEST 2008; 133:358–362)***

Key words: echocardiography; hospital mortality; logistic regression; prognosis; pulmonary embolism; right ventricular dysfunction

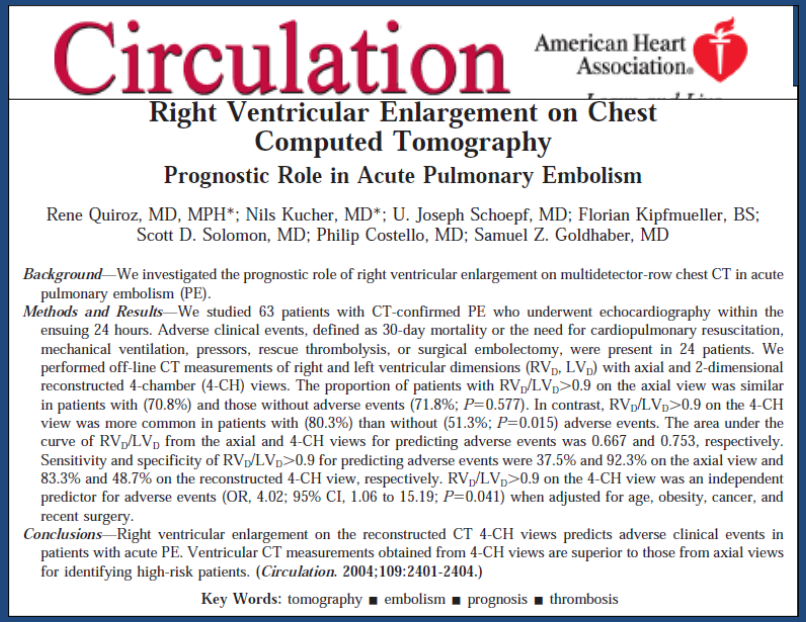
Abbreviations: CI = confidence interval; ICOPER = International Cooperative Pulmonary Embolism Registry; MAPPET = Management Strategies and Prognosis in Patients With Pulmonary Embolism; OR = odds ratio; ROC = receiver operating characteristic; RV/LV = right/left ventricular end-diastolic diameter

- Registry of 1,416 patients
- Mortality rate:
  - 1.9% if RV/LV ratio < 0.9
  - **6.6%** if RV/LV ratio ≥ 0.9

Fremont et al. CHEST 2008;133:358-362

Adverse outcomes associated with RVD

Patients with RVD defined as RV/LV >0.9 have a greater chance of adverse events within 30 days



Circulation

American Heart Association

Right Ventricular Enlargement on Chest Computed Tomography

Prognostic Role in Acute Pulmonary Embolism

Rene Quiroz, MD, MPH*; Nils Kucher, MD*; U. Joseph Schoepf, MD; Florian Kipfmueller, BS; Scott D. Solomon, MD; Philip Costello, MD; Samuel Z. Goldhaber, MD

Background—We investigated the prognostic role of right ventricular enlargement on multidetector-row chest CT in acute pulmonary embolism (PE).

Methods and Results—We studied 63 patients with CT-confirmed PE who underwent echocardiography within the ensuing 24 hours. Adverse clinical events, defined as 30-day mortality or the need for cardiopulmonary resuscitation, mechanical ventilation, pressors, rescue thrombolysis, or surgical embolectomy, were present in 24 patients. We performed off-line CT measurements of right and left ventricular dimensions (RV_D, LV_D) with axial and 2-dimensional reconstructed 4-chamber (4-CH) views. The proportion of patients with $RV_D/LV_D>0.9$ on the axial view was similar in patients with (70.8%) and those without adverse events (71.8%; $P=0.577$). In contrast, $RV_D/LV_D>0.9$ on the 4-CH view was more common in patients with (80.3%) than without (51.3%; $P=0.015$) adverse events. The area under the curve of RV_D/LV_D from the axial and 4-CH views for predicting adverse events was 0.667 and 0.753, respectively. Sensitivity and specificity of $RV_D/LV_D>0.9$ for predicting adverse events were 37.5% and 92.3% on the axial view and 83.3% and 48.7% on the reconstructed 4-CH view, respectively. $RV_D/LV_D>0.9$ on the 4-CH view was an independent predictor for adverse events (OR, 4.02; 95% CI, 1.06 to 15.19; $P=0.041$) when adjusted for age, obesity, cancer, and recent surgery.

Conclusions—Right ventricular enlargement on the reconstructed CT 4-CH views predicts adverse clinical events in patients with acute PE. Ventricular CT measurements obtained from 4-CH views are superior to those from axial views for identifying high-risk patients. (*Circulation.* **2004;109:2401-2404.**)

Key Words: tomography ■ embolism ■ prognosis ■ thrombosis

- Retrospective analysis of 63 patients with chest CT
- Adverse event rate at 30 days:
  - **80.3%** if RV/LV ratio > 0.9
  - **51.3%** if RV/LV ratio ≤ 0.9

Quiroz et. al. Circulation. 2004;109:2401-2404

Adverse outcomes associated with RVD

Presence of RV hypokinesis associated with 57% increase in mortality rate at 3 months

ARTICLES

Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER)

*Samuel Z Goldhaber, Luigi Visani, Marisa De Rosa, for ICOPER**

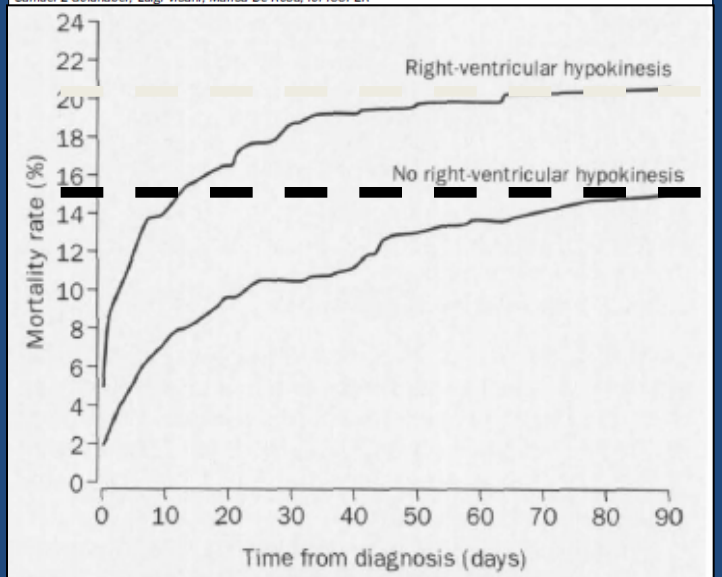


Figure 3: **Cumulative mortality according to status of right-ventricular function on baseline echocardiogram**

- Prospective study of 2,454 consecutive PE patients at 52 hospitals in 7 countries

Mortality rate at 3 months:

- **21%** with hypokinesis
- **15%** with no hypokinesis

Fremont et al. CHEST 2008;133:358-362

ANTICOAGULATION (AC) – HEPARIN

- AC therapy prevents further clot growth
- Studies[1-3] found:
- LMWH as effective as UFH in reducing recurrent PE
- LMWH carries reduced bleeding risk compared to UFH

STANDARD OF CARE: usually UFH or LMWH, followed by oral warfarin

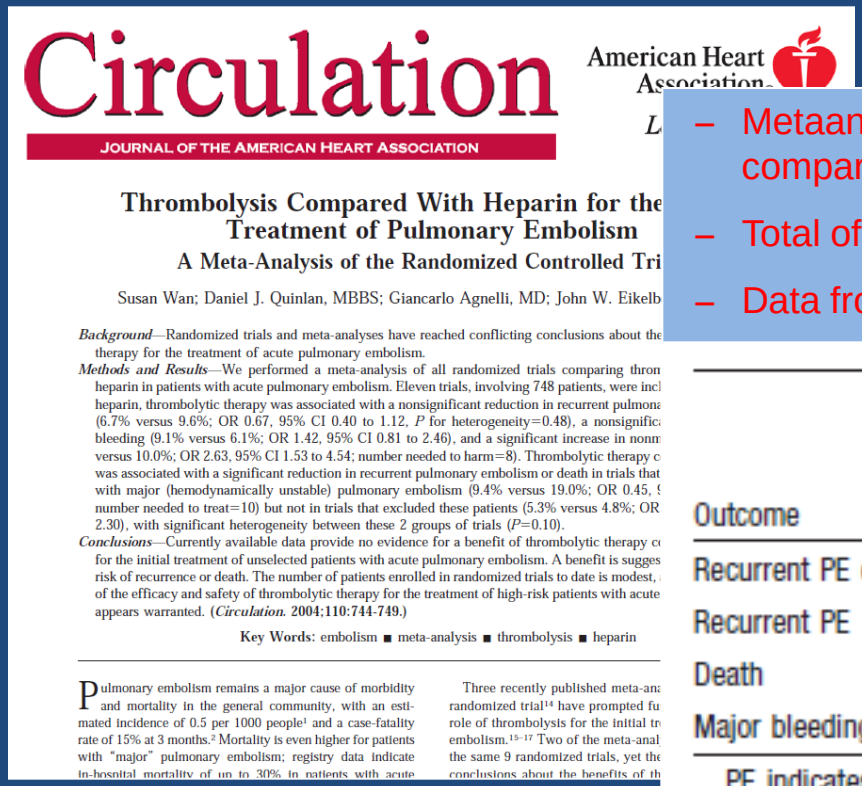
- However, AC therapy relies on endogenous t-PA to dissolve occluding clot[4]
  - **a process that typically occurs over several weeks or months**
  - **endogenous fibrinolysis may often be incomplete at the end**

1. Simonneau et al. N Engl J Med 1997;337:657-662.
2. Buller et al. N Engl J Med 2003;349:1695-17023.
3. Meyer et al. Thromb Heamost 1995;74:1432-1435
4. Arcasoy et al. Clin Chest Med 24 (2003) 73– 91.

IV thrombolysis with t-PA

- 100 mg t-PA infused over 2 hours
- Indicated for management of acute **massive** PE in adults:
  - For the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs.
  - For the lysis of pulmonary emboli accompanied by unstable hemodynamics, e.g., failure to maintain blood pressure without supportive measures.

Meta-analysis suggests reduced risk of recurrent PE or death from thrombolysis compared with heparin



Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Thrombolysis Compared With Heparin for the Treatment of Pulmonary Embolism

A Meta-Analysis of the Randomized Controlled Tri

Susan Wan; Daniel J. Quinlan, MBBS; Giancarlo Agnelli, MD; John W. Eikelb

Background—Randomized trials and meta-analyses have reached conflicting conclusions about the therapy for the treatment of acute pulmonary embolism.

Methods and Results—We performed a meta-analysis of all randomized trials comparing thron heparin in patients with acute pulmonary embolism. Eleven trials, involving 748 patients, were incl heparin, thrombolytic therapy was associated with a nonsignificant reduction in recurrent pulmona (6.7% versus 9.6%; OR 0.67, 95% CI 0.40 to 1.12, *P* for heterogeneity=0.48), a nonsignific bleeding (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46), and a significant increase in nonm versus 10.0%; OR 2.63, 95% CI 1.53 to 4.54; number needed to harm=8). Thrombolytic therapy c was associated with a significant reduction in recurrent pulmonary embolism or death in trials that with major (hemodynamically unstable) pulmonary embolism (9.4% versus 19.0%; OR 0.45, number needed to treat=10) but not in trials that excluded these patients (5.3% versus 4.8%; OR 2.30), with significant heterogeneity between these 2 groups of trials (*P*=0.10).

Conclusions—Currently available data provide no evidence for a benefit of thrombolytic therapy c for the initial treatment of unselected patients with acute pulmonary embolism. A benefit is sugges risk of recurrence or death. The number of patients enrolled in randomized trials to date is modest, of the efficacy and safety of thrombolytic therapy for the treatment of high-risk patients with acute appears warranted. (*Circulation.* **2004;110:744-749.**)

Key Words: embolism ■ meta-analysis ■ thrombolysis ■ heparin

Pulmonary embolism remains a major cause of morbidity and mortality in the general community, with an estimated incidence of 0.5 per 1000 people[1] and a case-fatality rate of 15% at 3 months.[2] Mortality is even higher for patients with "major" pulmonary embolism; registry data indicate in-hospital mortality of up to 30% in patients with acute

Three recently published meta-ana randomized trial[14] have prompted fu role of thrombolysis for the initial tr embolism.[15–17] Two of the meta-anal the same 9 randomized trials, yet the conclusions about the benefits of th

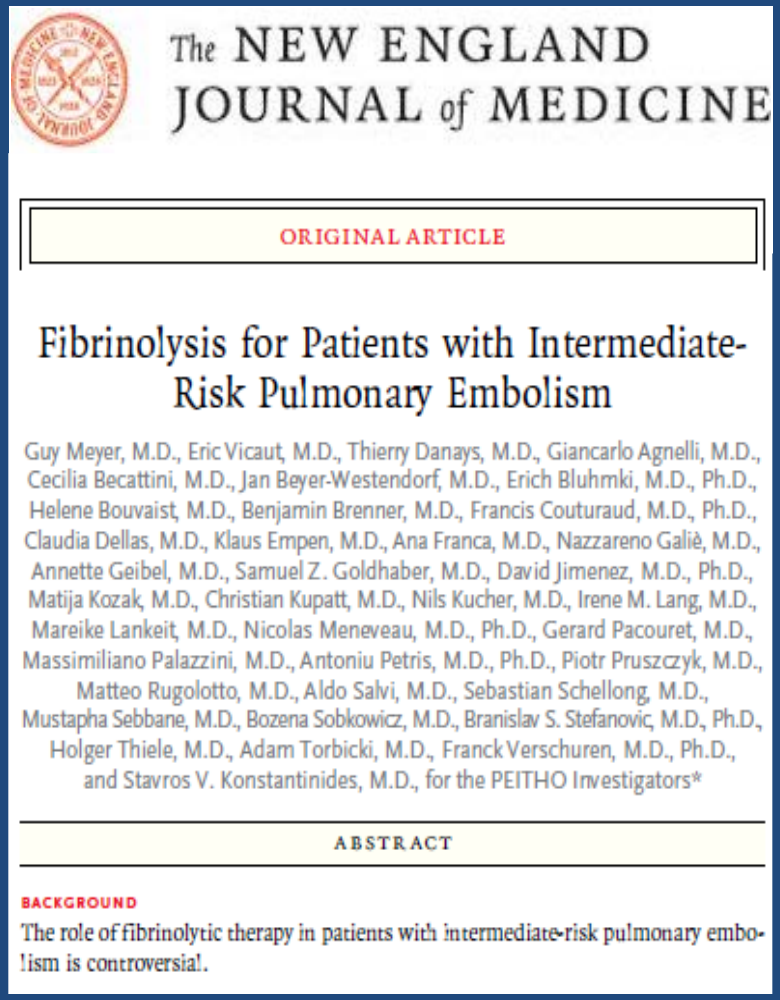
- Metaanalysis of randomized clinical trials for PE comparing thrombolytic therapy with heparin
- Total of 11 trials, 748 patients included
- Data from trials that included **massive** PE:

	Trials That Included Patients With Major PE		
Outcome	Thrombolysis, n/N (%)	Heparin, n/N (%)	OR (95% CI)
Recurrent PE or death	12/128 (9.4)	24/126 (19.0)	0.45 (0.22–0.92)
Recurrent PE	5/128 (3.9)	9/126 (7.1)	0.61 (0.23–1.62)
Death	8/128 (6.2)	16/126 (12.7)	0.47 (0.20–1.10)
Major bleeding	28/128 (21.9)	15/126 (11.9)	1.98 (1.00–3.92)

PE indicates pulmonary embolism.

Wan et al. Circulation. 2004 Aug 10;110(6):744-9.

Recent RCT examined benefit of IV thrombolysis in intermediate risk PE



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*

ABSTRACT

BACKGROUND

The role of fibrinolytic therapy in patients with intermediate-risk pulmonary embolism is controversial.

PEITHO Trial

Primary Objective:

– Investigate clinical benefits (efficacy) of thrombolysis with tenecteplase over placebo in **normotensive patients with acute intermediate-risk PE** (both treatment arms receive standard heparin anticoagulation)

Secondary Objective:

– To assess the safety of tenecteplase in patients with intermediate-risk PE

Meyer et al. N Engl J Med. 2014 Apr 10;370(15):1402-11

But the benefit of lysis came at the cost of major bleeds (including ICH)

	Tenecteplase (n=506)	Placebo (n=499)	P value
All strokes by day 7	12 (2.4%)	1 (0.2%)	0.003
– Hemorrhagic – Ischemic	10 2	1 0	
Serious adverse events (SAE)	29 (5.7%)	39 (7.8%)	0.19

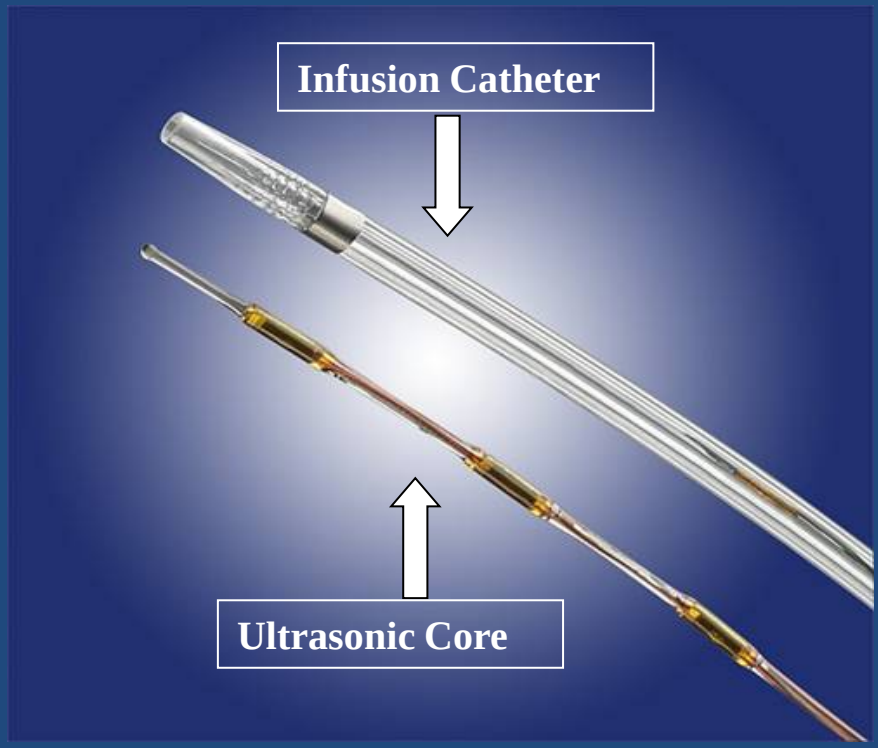
http://clinicaltrialresults.org/Slides/ACC%202013/Konstantinides_PEITHO_ACC%202013.pdf
Meyer et al. N Engl J Med. 2014 Apr 10;370(15):1402-11

Adoption of IV thrombolysis hampered by elevated risk of severe bleeds

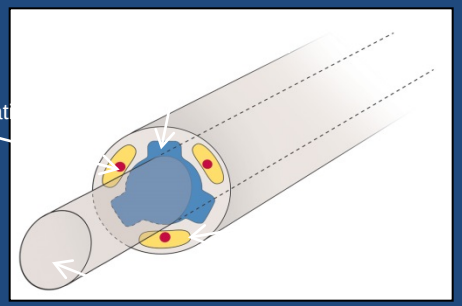
- In randomized trials, systemic PE thrombolysis is associated with a 13% risk of major bleeding and a 1.8% risk of intracranial hemorrhage[1]
- In clinical practice, systemic PE thrombolysis is associated with a 20% risk of major bleeding and a 3% risk of intracranial hemorrhage[2]
- In clinical practice, systemic thrombolysis is withheld in up to two thirds of patients with high-risk (massive) PE[3]

[1]*Eur Heart J 2008: 29:2276-2315*
[2]*Am J Cardiol. 2006;97:127-9*
[3]*Circulation 2006;113:577-82*

EkoSonic® Endovascular System



Therapy Optimizat

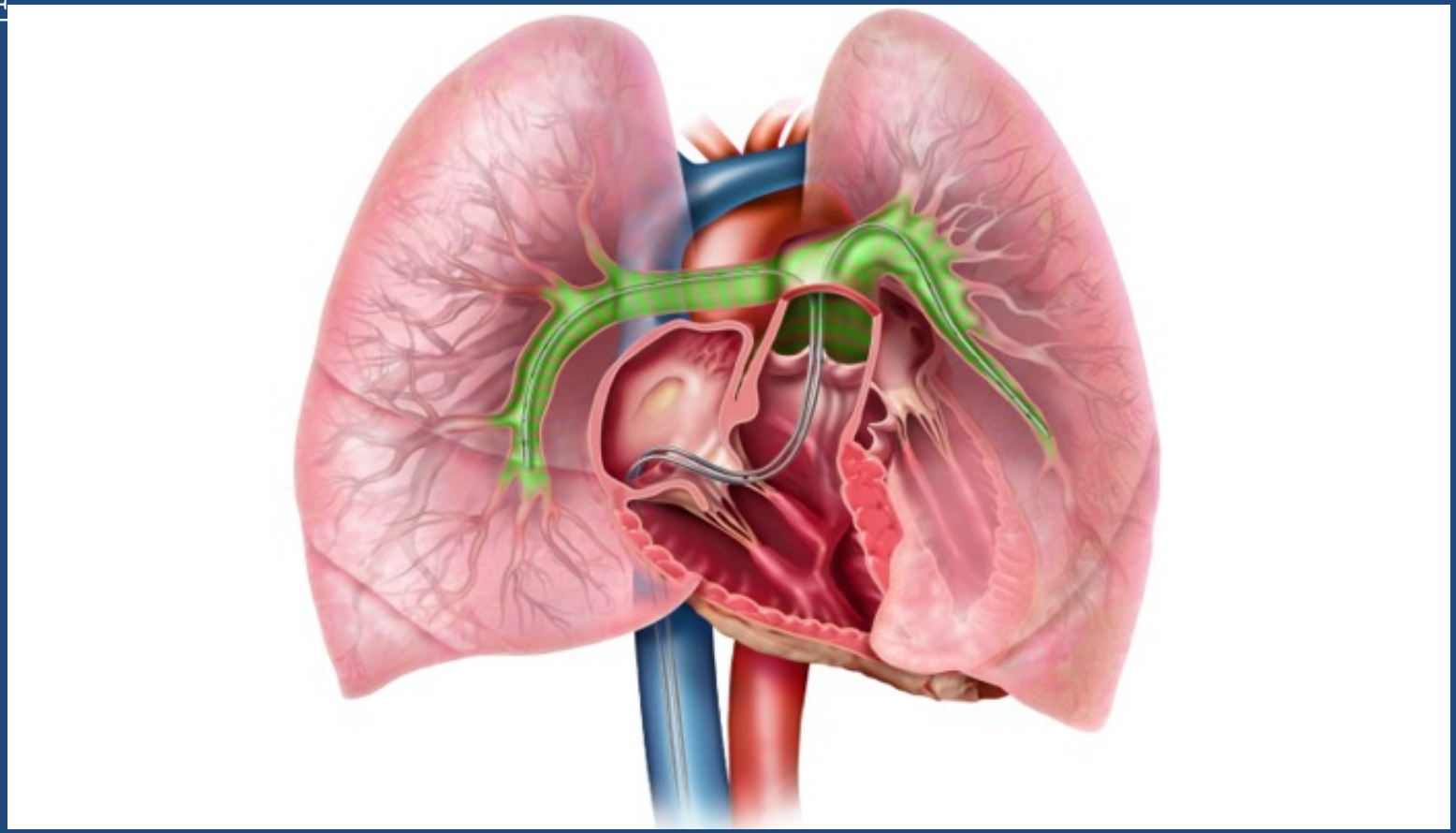


Features

- 5.4 Fr catheter
- 106 and 135 cm working length
- 6, 12, 18, 24, 30, 40 and 50 cm treatment zones

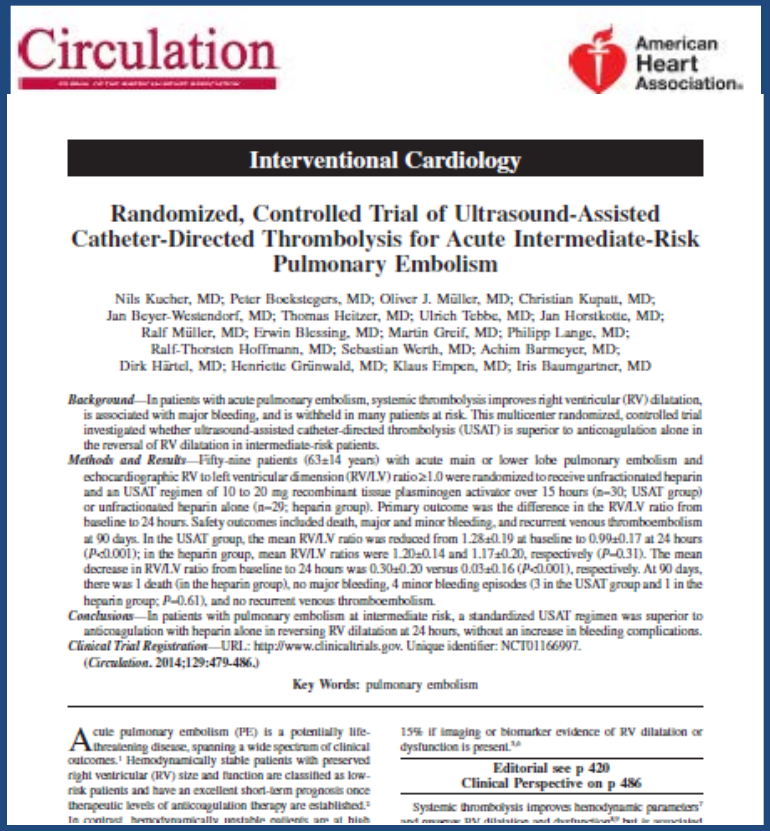
EkoSonic® Endovascular System

Placement in the left and right pulmonary arteries for the treatment of bilateral PE



ULTIMA study compared EKOS® to heparin in intermediate risk PE therapy

The first RCT for an advanced catheter-based modality



Circulation

American Heart Association.

Interventional Cardiology

Randomized, Controlled Trial of Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism

Nils Kucher, MD; Peter Boekstegers, MD; Oliver J. Müller, MD; Christian Kupatt, MD; Jan Beyer-Westendorf, MD; Thomas Heitzer, MD; Ulrich Tebbe, MD; Jan Horstkotte, MD; Ralf Müller, MD; Erwin Blessing, MD; Martin Greif, MD; Philipp Lange, MD; Ralf-Thorsten Hoffmann, MD; Sebastian Werth, MD; Achim Barmeyer, MD; Dirk Härtel, MD; Henriette Grünwald, MD; Klaus Empen, MD; Iris Baumgartner, MD

Background—In patients with acute pulmonary embolism, systemic thrombolysis improves right ventricular (RV) dilatation, is associated with major bleeding, and is withheld in many patients at risk. This multicenter randomized, controlled trial investigated whether ultrasound-assisted catheter-directed thrombolysis (USAT) is superior to anticoagulation alone in the reversal of RV dilatation in intermediate-risk patients.

Methods and Results—Fifty-nine patients (63±14 years) with acute main or lower lobe pulmonary embolism and echocardiographic RV to left ventricular dimension (RV/LV) ratio ≥1.0 were randomized to receive unfractionated heparin and an USAT regimen of 10 to 20 mg recombinant tissue plasminogen activator over 15 hours (n=30; USAT group) or unfractionated heparin alone (n=29; heparin group). Primary outcome was the difference in the RV/LV ratio from baseline to 24 hours. Safety outcomes included death, major and minor bleeding, and recurrent venous thromboembolism at 90 days. In the USAT group, the mean RV/LV ratio was reduced from 1.28±0.19 at baseline to 0.99±0.17 at 24 hours (P<0.001); in the heparin group, mean RV/LV ratios were 1.20±0.14 and 1.17±0.20, respectively (P=0.31). The mean decrease in RV/LV ratio from baseline to 24 hours was 0.30±0.20 versus 0.03±0.16 (P<0.001), respectively. At 90 days, there was 1 death (in the heparin group), no major bleeding, 4 minor bleeding episodes (3 in the USAT group and 1 in the heparin group; P=0.61), and no recurrent venous thromboembolism.

Conclusions—In patients with pulmonary embolism at intermediate risk, a standardized USAT regimen was superior to anticoagulation with heparin alone in reversing RV dilatation at 24 hours, without an increase in bleeding complications.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01166997.

(*Circulation*. 2014;129:479-486.)

Key Words: pulmonary embolism

Acute pulmonary embolism (PE) is a potentially life-threatening disease, spanning a wide spectrum of clinical outcomes.[1] Hemodynamically stable patients with preserved right ventricular (RV) size and function are classified as low-risk patients and have an excellent short-term prognosis once therapeutic levels of anticoagulation therapy are established.[2] In contrast, hemodynamically unstable patients are at high 15% if imaging or biomarker evidence of RV dilatation or dysfunction is present.[3,4]

Editorial see p 420
Clinical Perspective on p 486

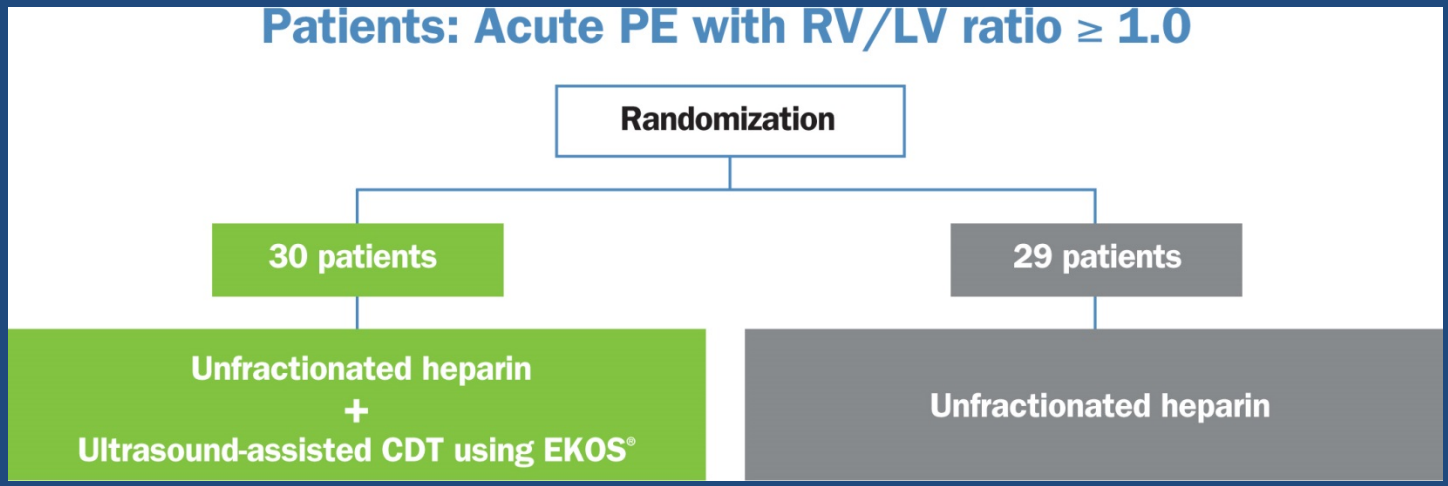
Systemic thrombolysis improves hemodynamic parameters[7] and reverses RV dilatation and dysfunction[8,9] but is associated

Primary Objective:

Determine whether fixed low-dose catheter-directed ultrasound accelerated thrombolysis is superior to heparin alone in reversal of RV dilatation in submassive / intermediate risk PE

Kucher et al. Circulation. 2014;129:479-486

RCT compared EKOS® to heparin for the treatment of intermediate risk PE



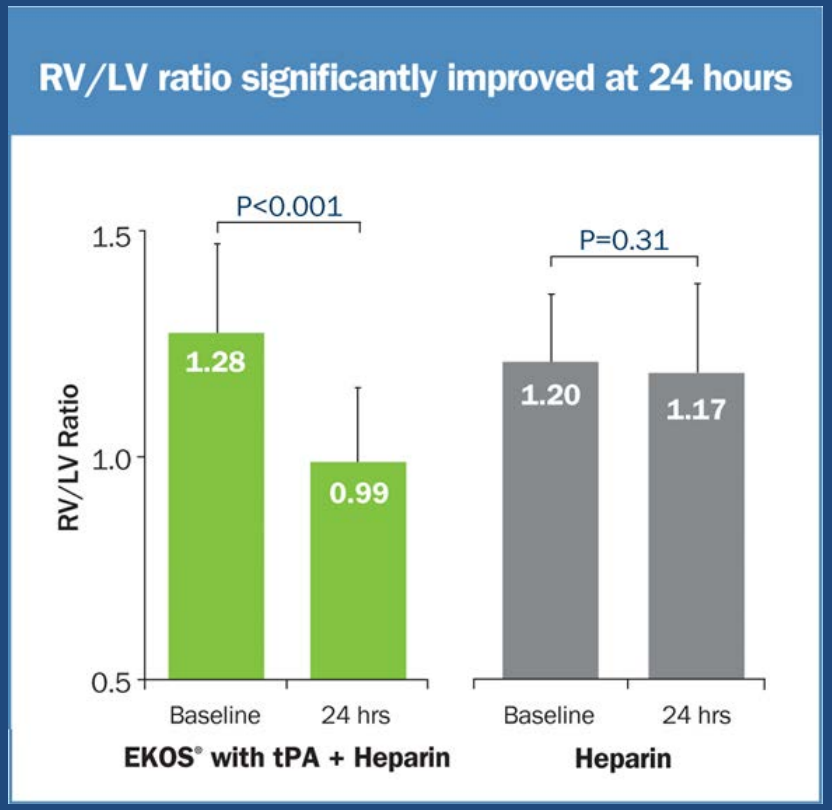
Infusion Protocol

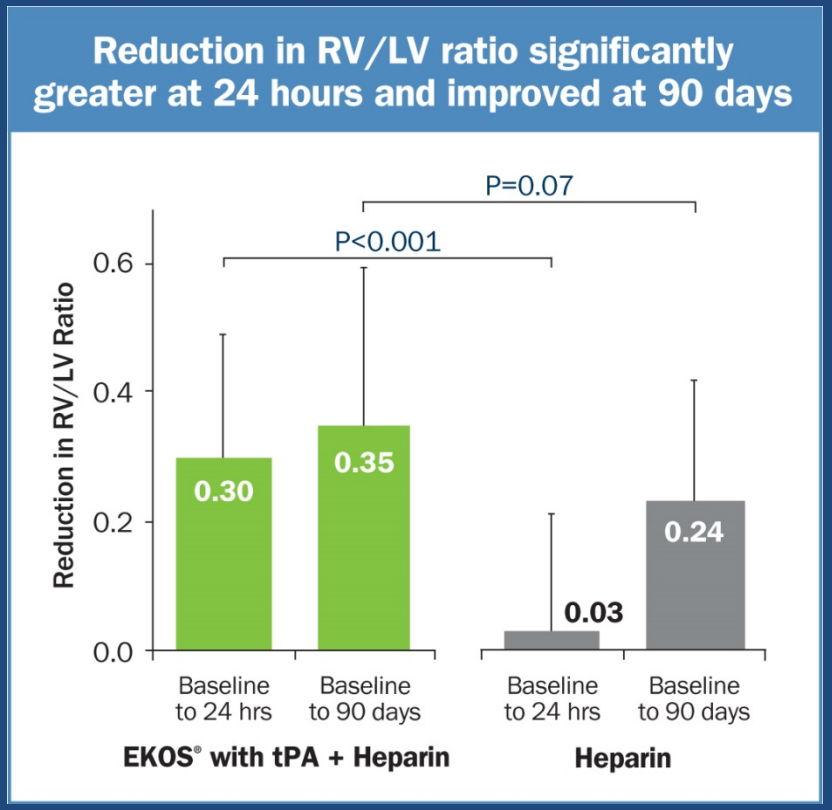
- rtPA 1mg/h; saline coolant 35ml/h
- Patients monitored in the intermediate or ICU
- After five hours, rtPA reduced to 0.5mg/h
- At 15 (+/- 1) hours, rtPA infusion, saline coolant and ultrasound discontinued
- EkoSonic® devices removed in the intermediate or ICU

- IV bolus: 80 IU/kg
- Infusion: 18 IU/kg/hour

Kucher et al. Circulation. 2014;129:479-486

tPA + heparin than with heparin alone





Kucher et al. Circulation. 2014;129:479-486

ULTIMA study

CONCLUSION

ULTIMA confirmed that a fixed-dose, ultrasound-assisted catheter-directed thrombolysis EKOS® regimen was superior to anticoagulation alone in improving RV dysfunction at 24 hours without an increase in bleeding complications.

SEATTLE II examined EKOS® benefit in a clinical trial setting in the US

Patients

Acute Massive and Submassive PE with RV/LV ratio ≥ 0.9 (n = 150; 22 centers)

Objectives

Evaluate ultrasound-facilitated, catheter-directed low-dose fibrinolysis:

- **Efficacy** – as measured by reduction in RV/LV ratio
- **Safety** – as measured by major bleeding within 72 hours

- Ultrasound-facilitated fibrinolysis using EKOS®
  - If unilateral PE: tPA 1 mg/hr using one device for 24 hours
  - If bilateral PE: tPA 1 mg/hr per device (using two simultaneously) for 12 hours
- Follow up at 48 +/- 6 hours
  - CT measurement of RV/LV ratio
  - Echocardiogram to estimate PA systolic pressure

Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

Endpoints

- Primary Efficacy
  - Change in core lab-measured RV/LV ratio from baseline to 48 hours as assessed by chest CT
- Secondary Efficacy
  - Change in invasively measured PA systolic pressure from baseline to device removal and as estimated on 48-hour echocardiogram
- Primary Safety
  - Adjudicated major bleeding within 72 hours of the start of the procedure

Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

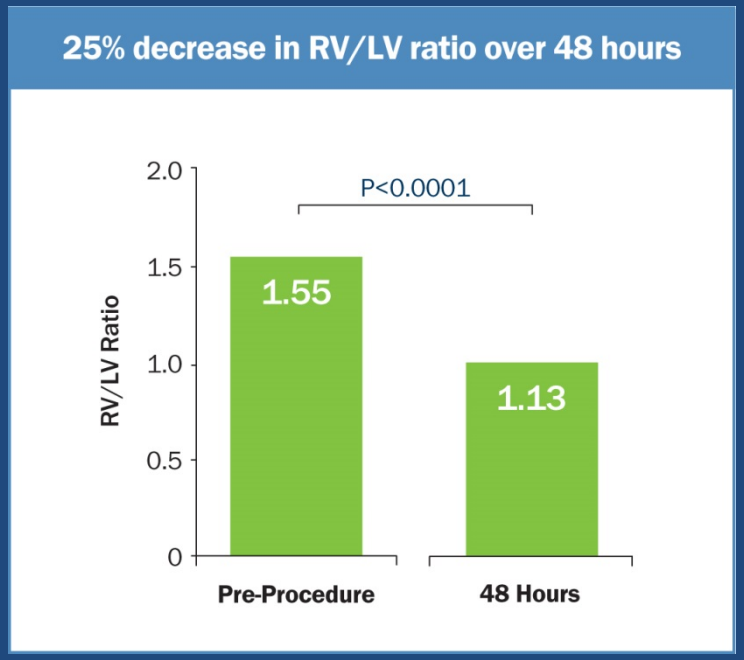
Patient characteristics and treatment details

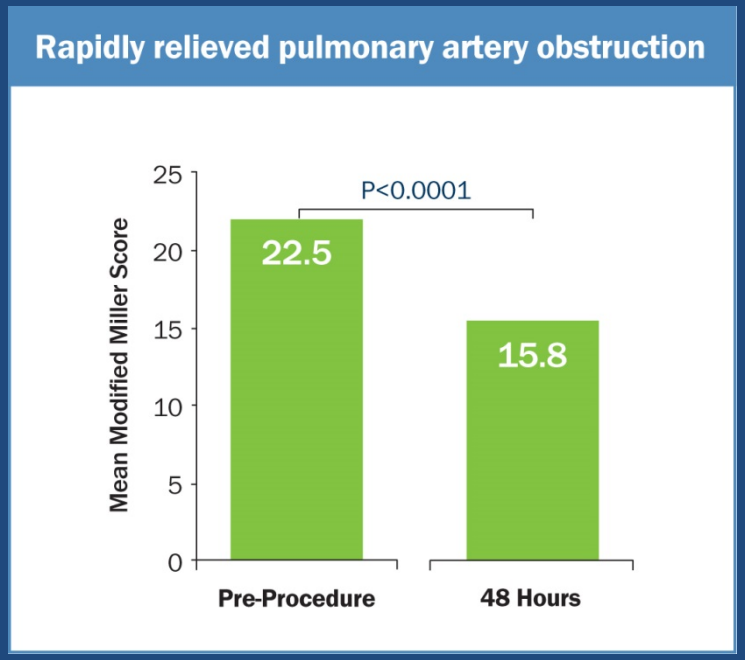
	N	%
Total enrollment	150*	100%
Massive / Submassive PE	31 / 119	21% / 79%
History of previous DVT	30	20%
History of previous PE	15	10%
Concomitant use of antiplatelet agents	51	34%
Unilateral / Bilateral PE	20 / 130	13% / 87%
Total rtPA dose	**23.7 ± 2.9 mg**	

* Denotes 1 patient died prior to treatment

Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

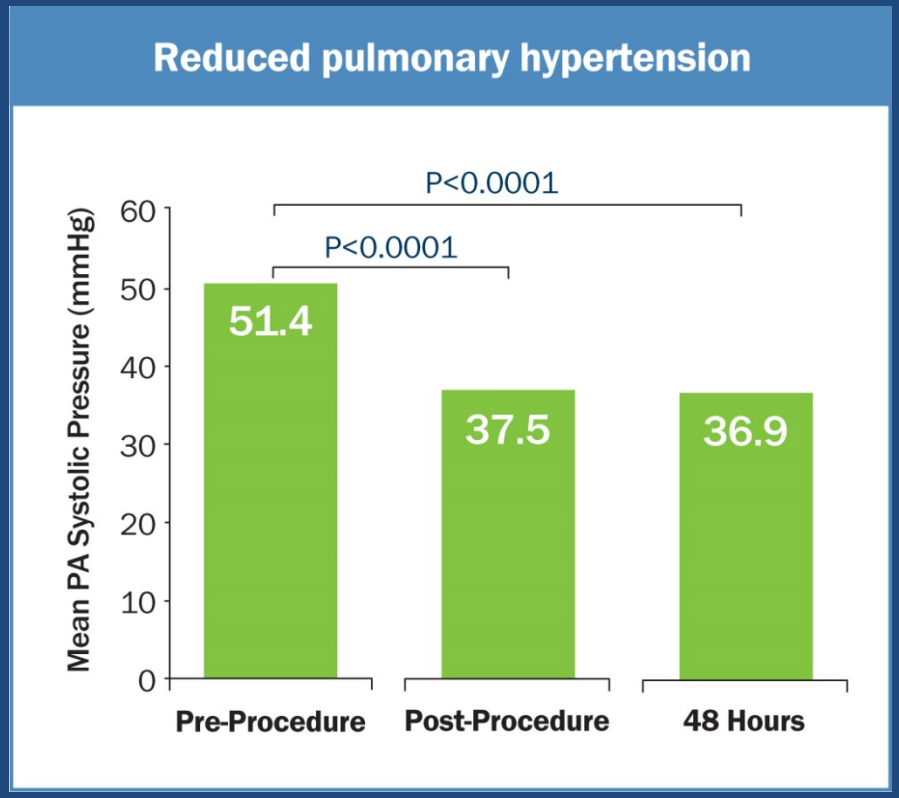
Reduced RV/LV ratio and Modified Miller Score at 48 hours post-EKOS®





Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

Reduced pulmonary artery pressure immediately post-procedure



Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

Clinical outcomes*	N = 150
Mean length of stay ± SD, days	8.8 ± 5
In-hospital death, n (%)	3 (2)
30-day mortality**, n (%)	4 (2.7)
Serious adverse events due to device, n (%)	2 (1.3)
Serious adverse events due to t-PA, n (%)	2 (1.3)
IVC filter placed, n (%)	24 (16)
Major bleeding within 30 days**, n (%)	17 (11.4)
GUSTO moderate**	16 (10.7)
GUSTO severe**	1 (0.7)
Intracranial hemorrhage, n (%)	0 (0)

*All death, serious adverse and bleeding events were adjudicated by an independent safety monitor
**N = 149 (1 patient lost to follow-up)

Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

Minimized risk of intracranial hemorrhage

Study	Intracranial Hemorrhage (Fibrinolysis Group)
ICOPER (Goldhaber SZ, et al. 1999)	9/304 (3%)
PEITHO (Meyer G, et al. 2014)	10/506 (2%)
SEATTLE II (Piazza G, et al. 2014)	0/150 (0%)

Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

SEATTLE II study

CONCLUSION

Ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute PE improves RV function and decreases pulmonary hypertension and angiographic obstruction. By minimizing the risk of intracranial bleed, it represents a potential "game-changer" in the treatment of high-risk PE patients.

Piazza G. "A Prospective, Single-Arm, Multicenter Trial of Ultrasound-Facilitated, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II)." American College of Cardiology 63rd Annual Scientific Session, Washington DC, March 30, 2014.

Summary

- RV dysfunction in PE patients predicts poor outcomes:
  - Mortality
  - Adverse events
  - VTE recurrence
- Anticoagulant therapy does not actively resolve the existing thrombus
- IV thrombolysis is not used broadly:
  - Clinical data show improvement in hemodynamics,
  - but it carries an elevated risk of severe bleeding, including ICH

Summary

- Use of EKOS® enhances thrombolytic therapy by an intra-catheter ultrasound technology, which:
  - Loosens the fibrin structure
  - Increases drug penetration into the fibrin matrix
  - Ultimately reduces drug dose, treatment time and risk of complications
- Clinical data establish the evidence for EKOS® in massive and submassive (intermediate risk) PE:
  - ULTIMA – prospective, randomized, controlled, multicenter trial
  - SEATTLE II – prospective, controlled, multicenter trial
  - Single-center studies
  - One metaanalysis

Summary

- Consistent EKOS® results among the various published studies:
  - Restoration of hemodynamics as evidenced by a reduced RV/LV ratio and decreased PA pressure
  - Resolution of pulmonary artery obstruction
  - Favorable outcomes with low dose thrombolysis (20-24 mg tPA based on the clinical trials)
  - No reports of intracranial hemorrhage in published clinical studies

Early study showed safer and more effective lysis with EKOS® than CDT

- Single center retrospective comparative study
- 25 patients with massive pulmonary embolism (PE) were treated with either EKOS® or catheter directed thrombolysis (CDT) without ultrasound.
- 11 patients received EKOS® therapy for 15 PE lesions
- 14 patients received CDT therapy for 18 PE lesions

	EKOS® (n=11)	CDT (n=14)	P value
Complete thrombolysis	100%	50%	0.01
Thromboyltic dose (tPA, mg)	17.2 ± 2.36	25.43 ± 5.27	0.03
Bleeding complications	0%	21.4%	0.02

Lin et al. Vascular. 2009 Nov-Dec;17 Suppl 3:S137-47

- Single center retrospective single arm study
- 24 patients with high risk (n=5) or intermediate risk (n=19) PE treated with EKOS®
- Mean rtPA dose was 33.5±15.5 mg over 19.7 hours

	Pre-EKOS®	Post-EKOS®	P value
RV/LV ratio	1.33 ± 0.24	1.00 ± 0.13	<0.001
Modified Miller Score	17.8 ± 5.3	8.7 ± 5.1	<0.001

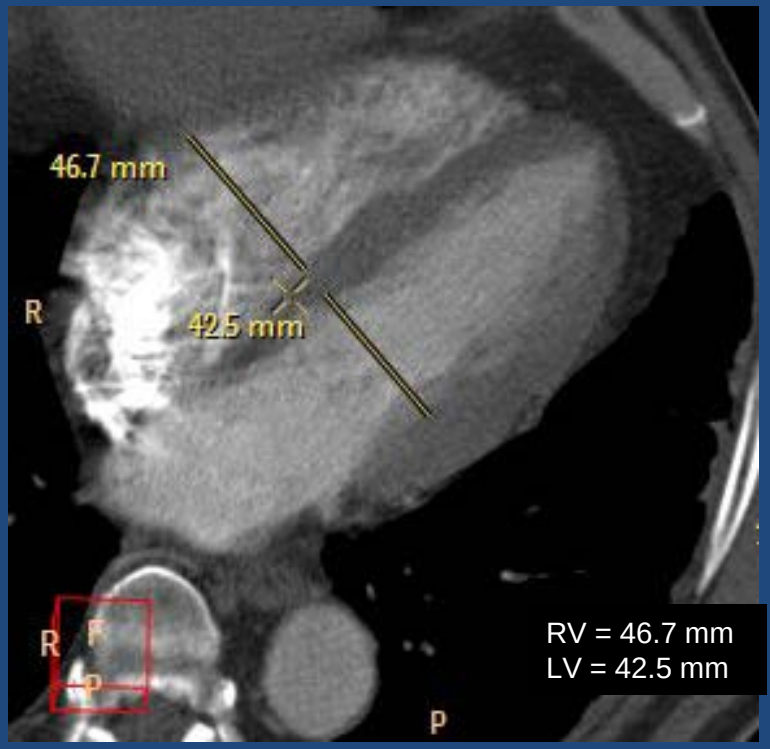
- No deaths or systemic bleeding complications, including intracranial hemorrhage; 4 access site bleeds requiring transfusion

Engelhardt et al. Thromb Res. 2011 Aug;128(2):149-54.

Single center experience showed CTA evidence of RVD resolution

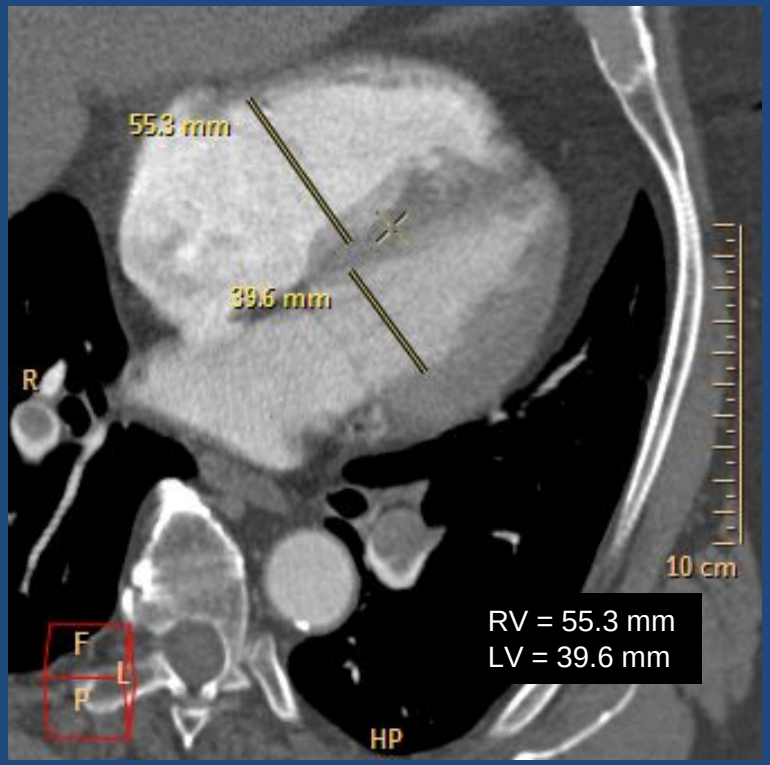
Case study 1

Pre-treatment:
RV/LV = 1.64

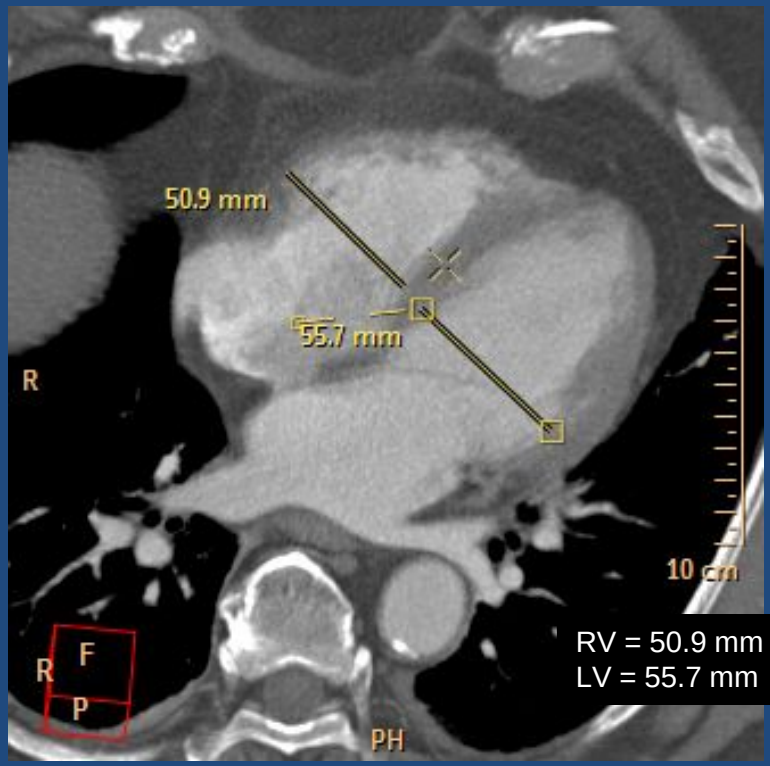


Post-treatment
RV/LV = 1.10

Case study 2



Pre-treatment
RV/LV = 1.40



Post-treatment
RV/LV = 0.91

Important Facts about Venous Insufficiency!!

- When left untreated, venous reflux can lead to significant clinical issues, like pain, swelling, varicose veins, skin changes, and ulcers AND hemodynamic and neuro-hormonal derangements that can make heart failure and Hypertension worse (THAT'S THE MISSING LINK!!!!)

Important Facts about Venous Disease!!

- Although up to 50% of patients with DVT, are ASYMPTOMATIC, all are at risk for PUMONARY EMBOLISM!!!!!!!!!!

- Statistics show that of the 25 million people in the U.S. who suffer from symptomatic venous insufficiency, only about 5% seek treatment annually; 2/3 of patients who do seek treatment have Great saphenous vein reflux!! (Easy to treat!)

Manifestations of Venous Insufficiency

Superficial venous reflux is progressive and if left untreated, may worsen over time.
Below are manifestations of the disease.[5]

Varicose Veins	Swollen Legs	Skin Changes	Skin Ulcers
			
20+ million	2 to 6 million		500,000

Photos courtesy of Rajabrata Sarkar, MD, PhD.

CEAP Classifications

Clinical Classifications of Venous Insufficiency (CEAP)

- Class 0 - No visible or palpable signs of venous disease
- Class 1 - Telangiectasias or reticular veins
- Class 2 - Varicose veins
- Class 3 - Edema
- Class 4 - Skin changes
    - (4a) Skin changes including pigmentation or venous eczema
    - (4b) Skin changes with lipodermatosclerosis
- Class 5 - Healed venous ulceration
- Class 6 - Active venous ulceration

Cutaneous Chain of Events

- Edema and induration
- Pigmentation
- Dermatitis
- Atrophie blanche
- Ulceration
- Infection
- Further complications

Accessory Saphenous Vein Reflux

Edema and Hyperpigmentation

Image courtesy of Rajabrata Sarkar, MD

- Lower leg edema and hyperpigmentation are common presentations with venous insufficiency

Progression of Venous Stasis

- Poor skin nutrition and oxygenation
- Subcutaneous fat necrosis
  - Lipodermatosclerosis
  - Venous stasis ulceration
    - Will recur unless underlying venous insufficiency is treated

Photo source: Amor Khachemoune, Catharine Lisa Kauffman: Management Of Leg Ulcers. *The Internet Journal of Dermatology.* 2002. Volume 1 Number 2.

Atrophie Blanche

- Characterized by:
  - Ivory-white, smooth, atrophic scar tissue with telangiectasia
  - Within a hyperpigmented areola
  - Usually occurring on the ankles of middle-aged women

Image courtesy of Charles Dietzek, DO

Venous System

- Venous blood flows from the capillaries to the heart
- Flow occurs against gravity
  - Muscular compression of the veins
  - Negative intrathoracic pressure
  - Calf muscle pump
- Low flow, low pressure system

Venous System

- Deep venous system
- Superficial venous system
  - Saphenous veins
  - Lateral venous complex
- Perforating veins

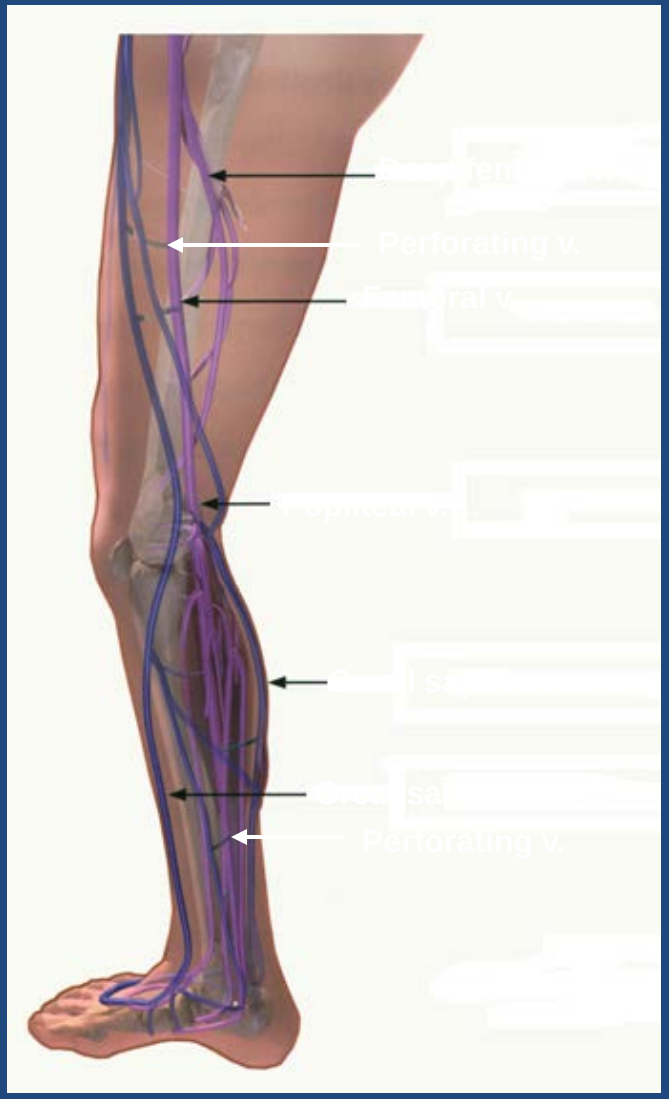


Image source: Fundamentals of Phlebology: Venous Disease for Clinicians. Illustration by Linda S. Nye. American College of Phlebology 2004.

Anatomic Overview – Calf Muscle Pump

- Muscles enclosed in fascial envelope
- Muscular contraction raises pressure
- Venous compression occurs
- Vein valves affect direction of flow

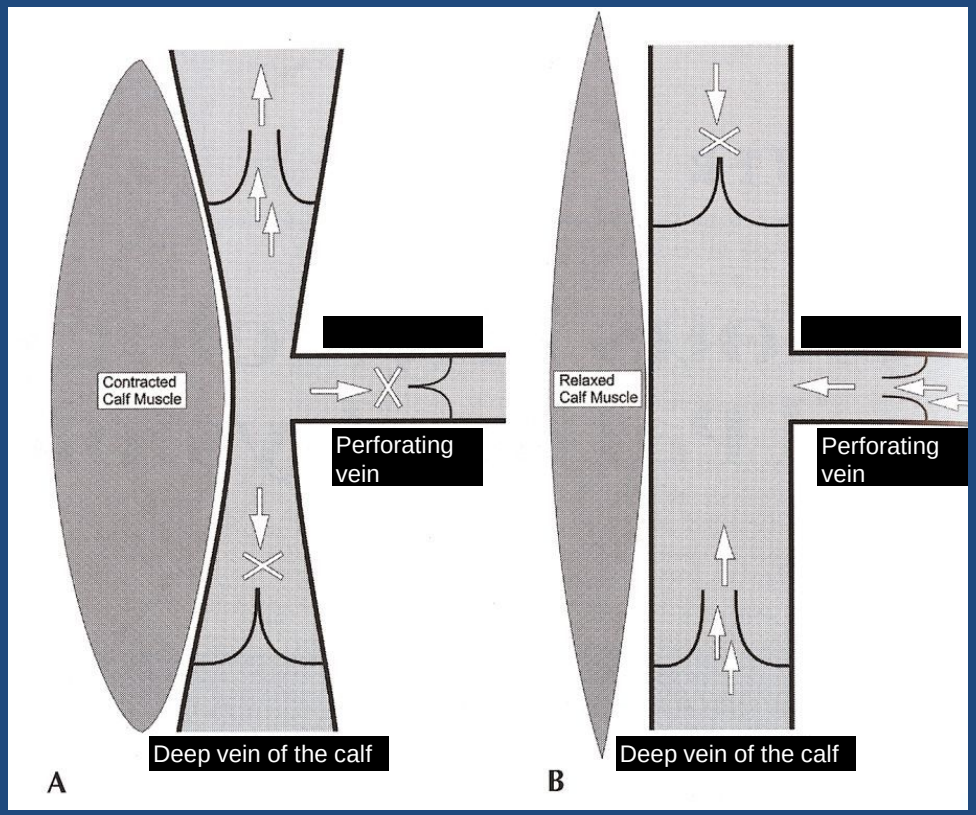
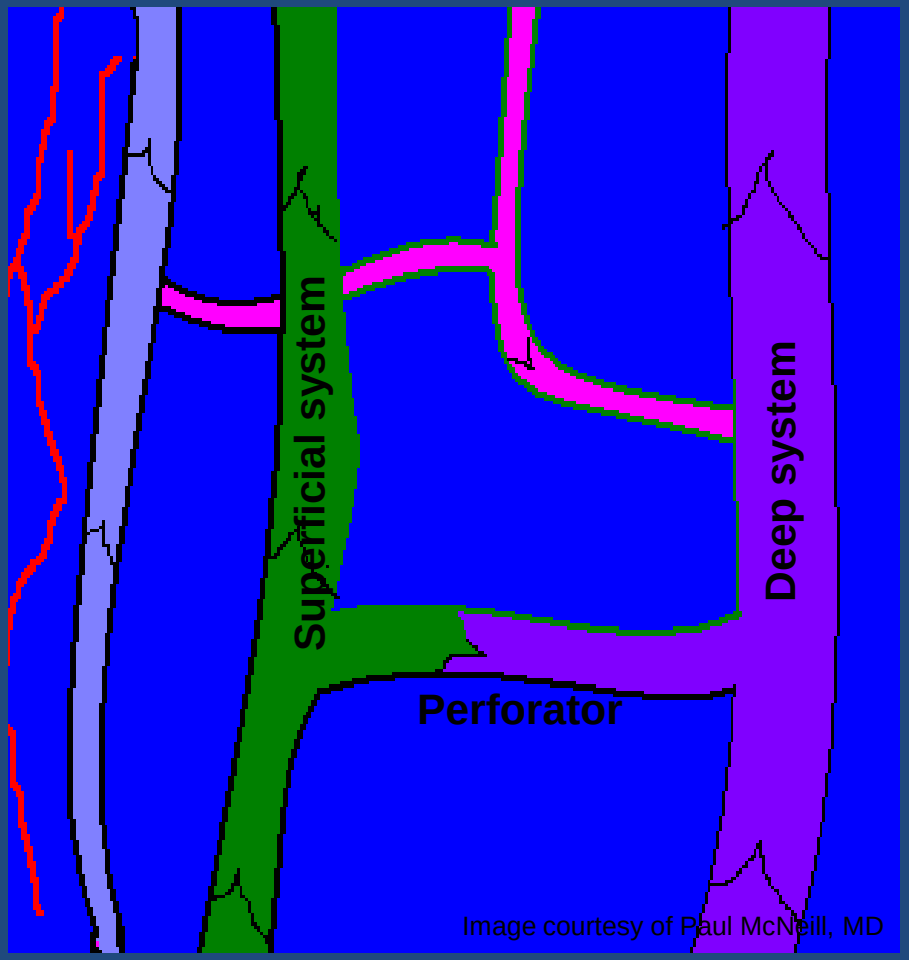


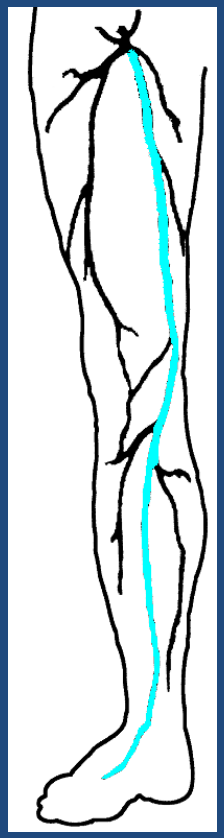
Image source: Weiss RA, et al eds. *Vein diagnosis and treatment: A comprehensive approach*. McGraw-Hill Companies, Inc.; 2001.

Normal Function

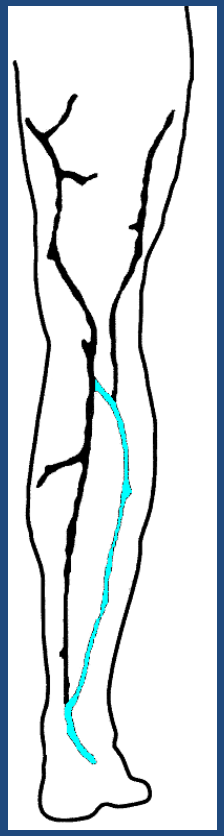


- Relationship of superficial veins and GSV vein valves
- Normal caliber of veins throughout system
- Low pressure maintained

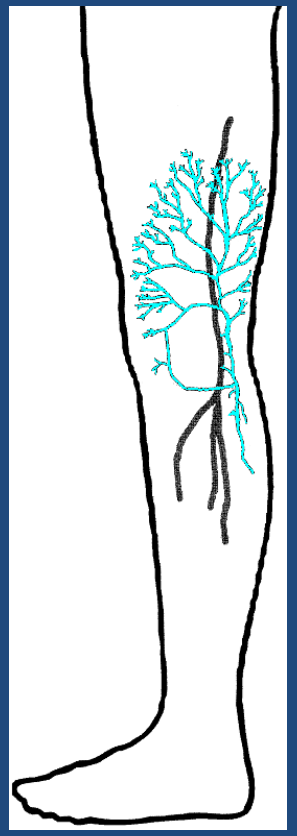
Superficial Venous System



Great
Saphenous Vein



Small
Saphenous Vein



Lateral Venous
Complex

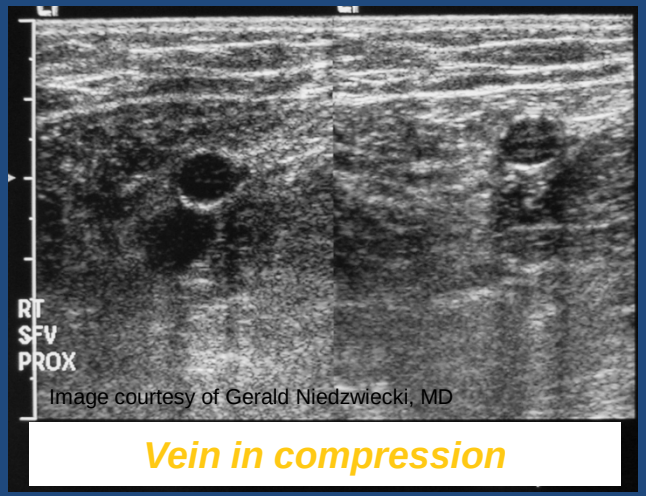
Images adapted from: Thorisson HM et al. The role of ultrasound in the diagnosis and treatment of chronic venous insufficiency. Ultrasound Quarterly 2007;23:137-50.

Duplex Ultrasound in Diagnosis and Treatment of Venous Disease

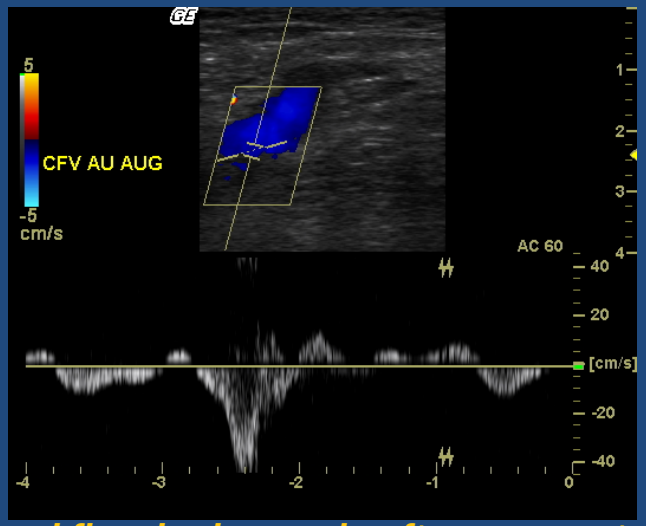
Reflux Assessment
Deep System Exam

- Assess deep venous system and rule out DVT using compression, color flow and augmentation

- Note areas of deep system incompetence at this time



Vein in compression



Normal flow in deep vein after augmentation

Reflux Assessment

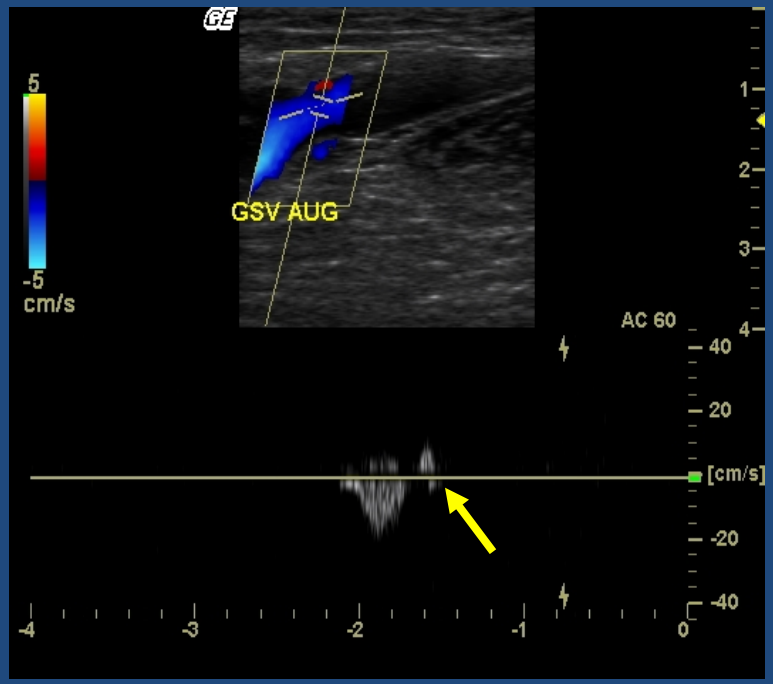
Superficial System Exam

- Evaluation for reflux
  - Doppler samples taken at:
    - SFJ
    - Multiple sites along saphenous
  - Valsalva is helpful at the SFJ for reflux
    - Below that, augmentation should be used
  - Reflux is noted as the reversal of flow after augmentation (usually ≥0.5 seconds)[1]

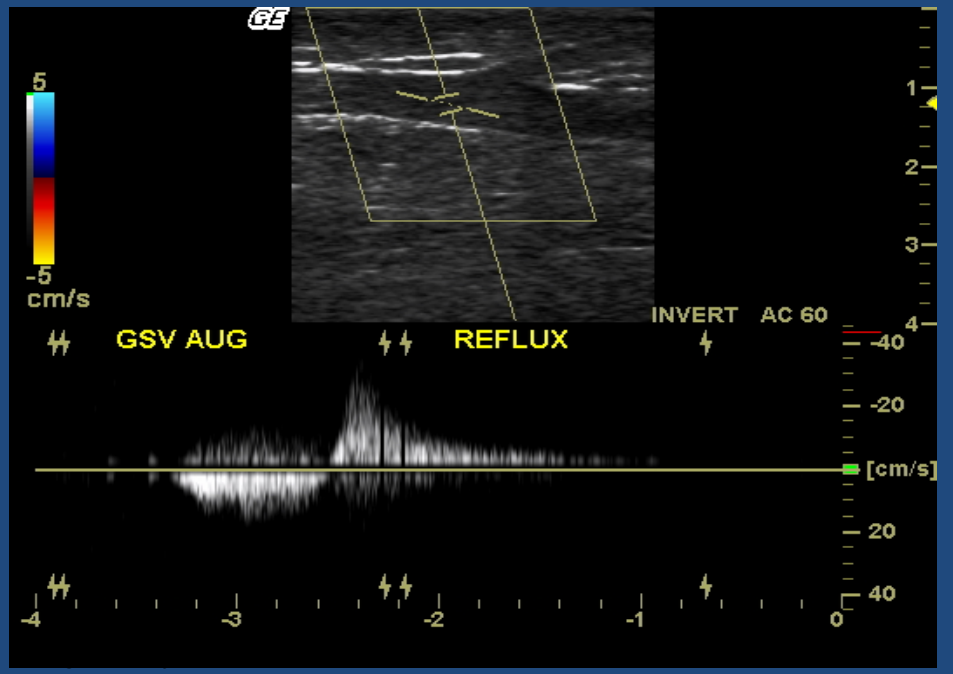
1. Reference: Masuda EM, Kistner RL, Eklof B. Prospective study of duplex scanning for venous reflux: comparison of Valsalva and pneumatic cuff techniques in the reverse Trendelenburg and standing positions. J Vasc Surg -1994 Vol. 20 711-20

Superficial System Exam

Great Saphenous Vein

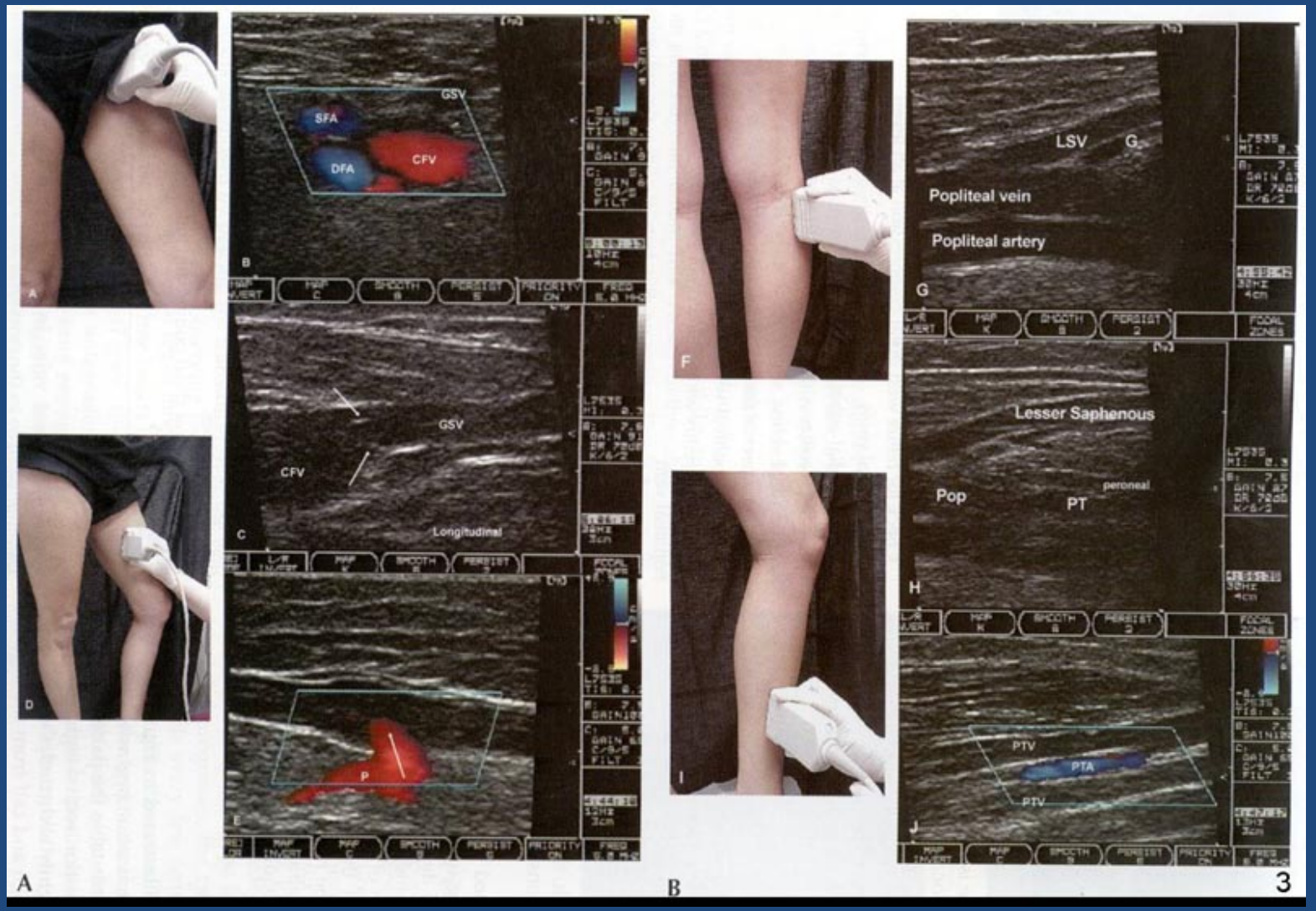


Normal valve closure time of <0.5 sec

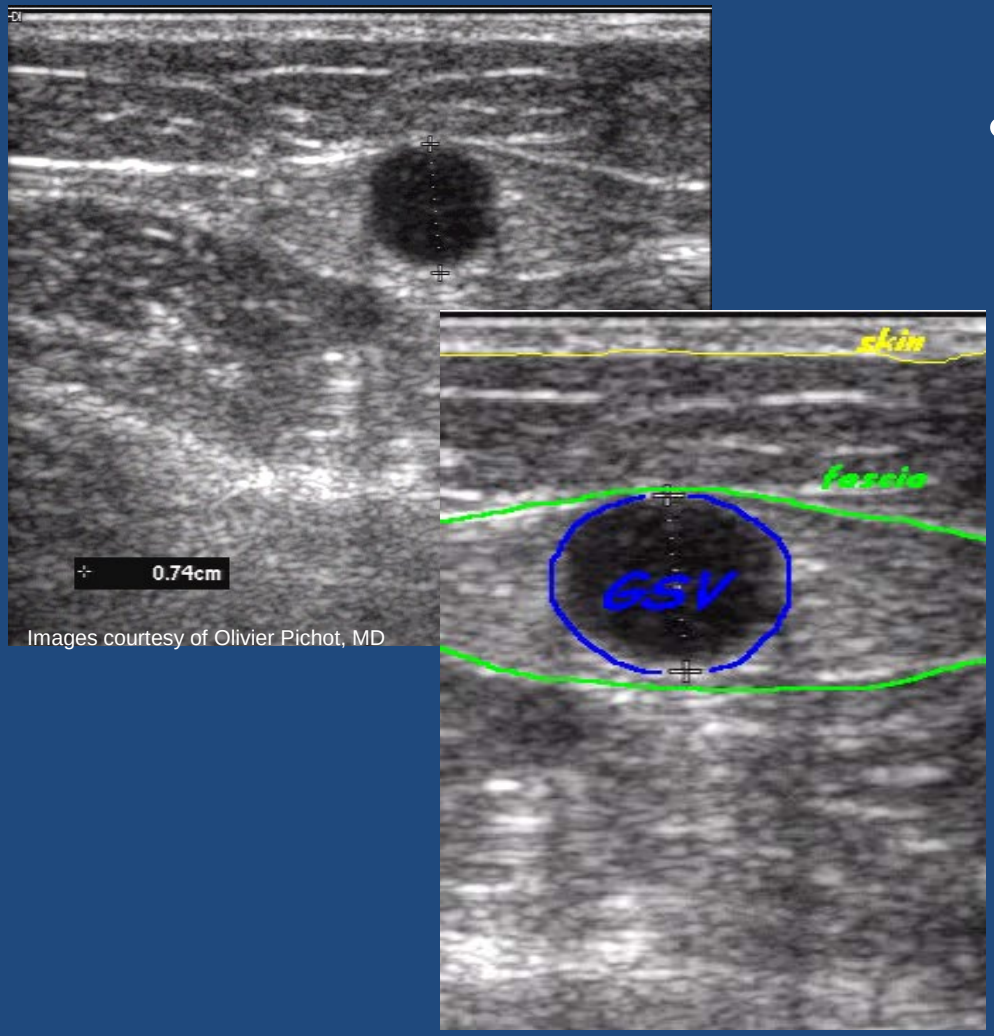


Reflux of approximately 1.5 seconds

Insufficiency Exam



The Great Saphenous Vein



Images courtesy of Olivier Pichot, MD

- GSV within the fascial envelope
  - Note the superficial or saphenous fascia above the vessel and the deep or muscular fascia below the vessel

Treatment Options

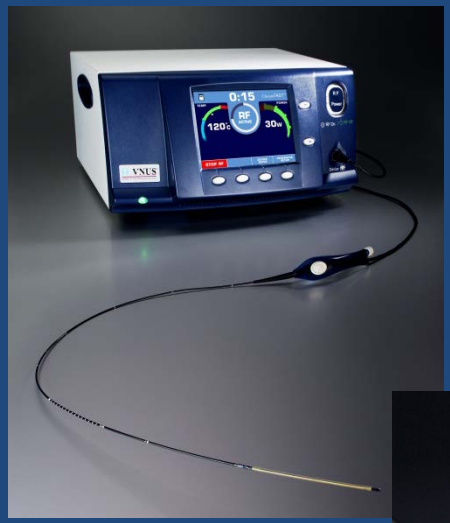
- Ignore or dismiss
  - The most common option
- Diuretics, fluid and salt restriction
  - Minimal effect on venous pressure at the ankle
- Compression hose
  - Partial counterforce to venous hypertension
  - Doesn’t impact underlying pathophysiology
- High ligation and stripping of the GSV
- Endovascular ablation of the GSV

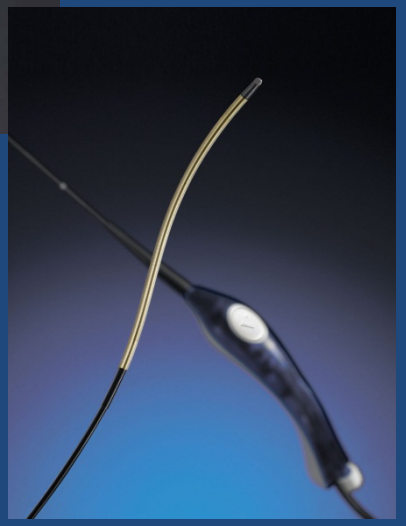
High Ligation and Stripping

- Traditionally viewed as the “gold standard”
  - Inpatient procedure
  - General anesthesia required
  - Initial failure due to
    - Stripping of wrong vein (medial or lateral accessory)
    - Failure to strip *all* large, incompetent veins
  - Late failure (35-50%) due to development of neovascular venous clusters and re-creation of original pathophysiology
  - ~ one third of patients require a second surgical procedure

The VNUS Closure® System

- The VNUS Closure System is a minimally invasive treatment alternative for patients with symptomatic superficial venous reflux and varicose veins
- Using a catheter-based approach, the VNUS ClosureFAST™ catheter delivers radiofrequency (RF) energy to the vein wall
- RF energy creates conductive *heating* that contracts the vein wall collagen, thereby occluding the vein





Efficacy of the ClosureFAST™ Catheter

The ClosureFAST™ catheter ablates the vein in 7cm segments with 20-second treatment cycles, resulting in vein shrinkage and occlusion.

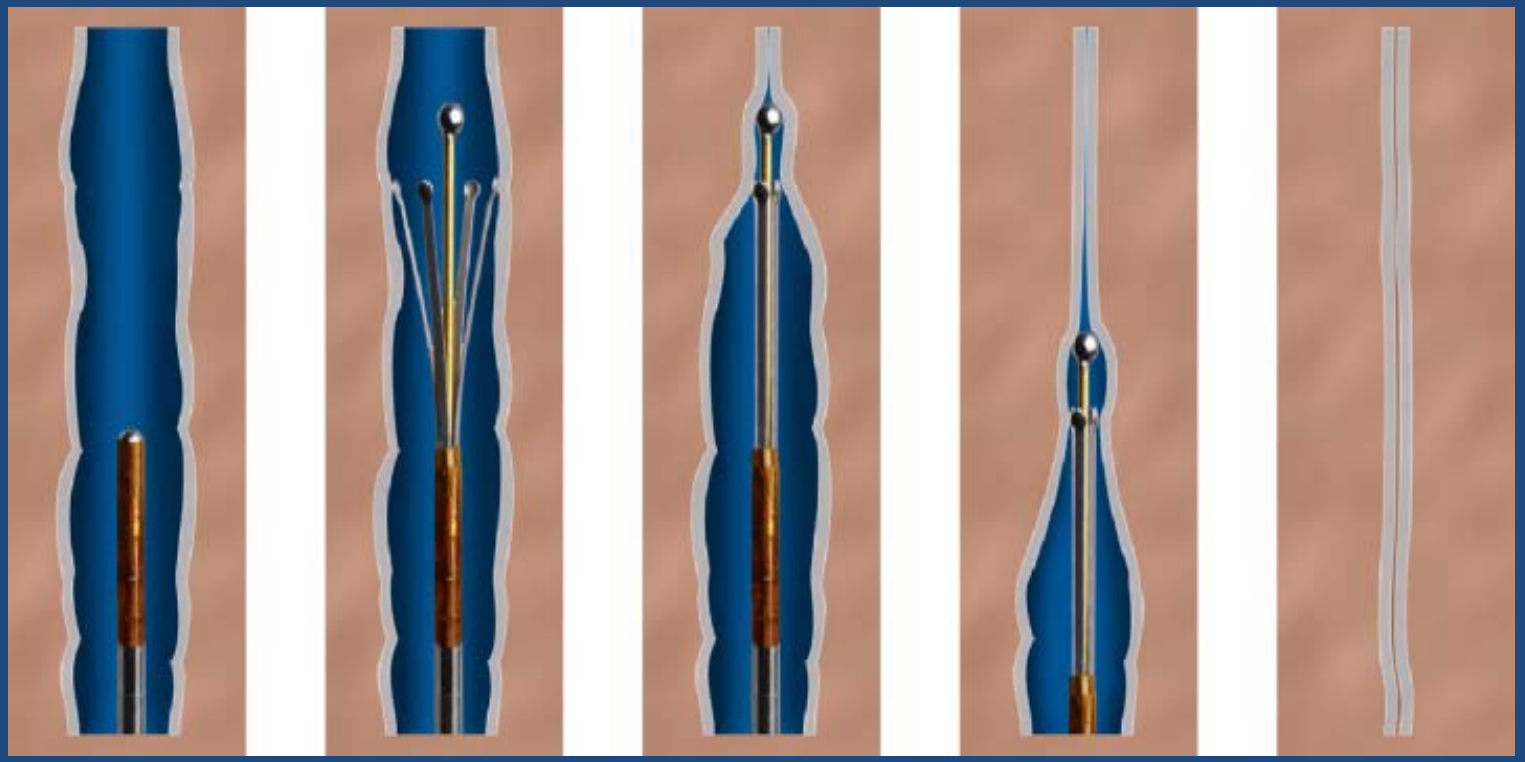
Interim data from a multicenter prospective study have shown 97.4% vein occlusion 1 year post-treatment.[6]

Perivenous Tumescent Infiltration

- Dilute local anesthetic infiltrated into saphenous compartment (perivenously) using duplex imaging

Perivenous infiltration technique:
note 360° “halo” of fluid around vein

The Closure Procedure



Catheter inserted in refluxing vein

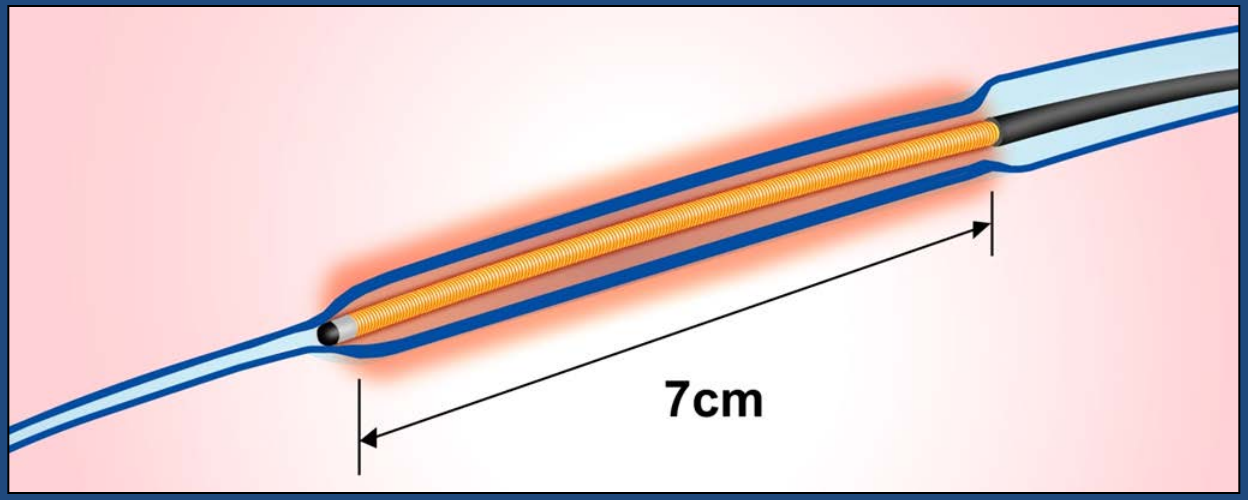
Catheter Positioned, Electrodes deployed

RF Energy heats and contracts vein wall

Catheter slowly withdrawn, closing vein

Denuded vein is physically narrowed

Closure*FAST*
Segmental Ablation



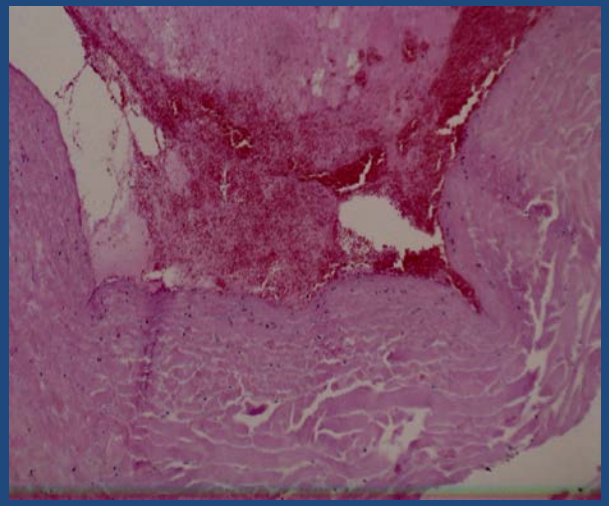
- 7 cm length treated all at once in 20 seconds
  - Device (set) temperature: 120° C
  - Tissue temperature: 100 - 110° C
- No energy delivery during repositioning
- Uniform energy dose not dependant on pullback speed

Radiofrequency Ablation
Mechanism of Action

- Temperature controlled direct heating of vein wall
- Vein wall collagen contraction
- Endothelial cell denudation
- Inflammatory swelling of vein wall
- Fibrotic seal of vein lumen

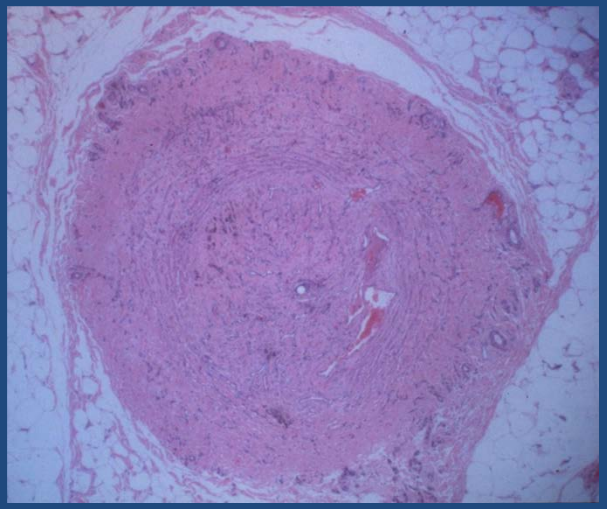
Acute result

Immediate and Intermediate Effect of RFA



Endothelial cell denudation[2]
(acute result)

Vein wall collagen denatures and continuous physical contraction occurs[2]
(acute result)



Fibrotic occlusion results[3]
(6 week follow up)

Venous Disease

The Missing Link in Cardiovascular Medicine

- Historically, Venous disease (chronic venous insufficiency, DVT, and varicose veins), for most part, has been the domain of vascular surgeons.

- It’s only 3 or 4 years since Interventional Cardiologist have become involved in this field.

Venous Disease

The Missing Link in Cardiovascular Medicine

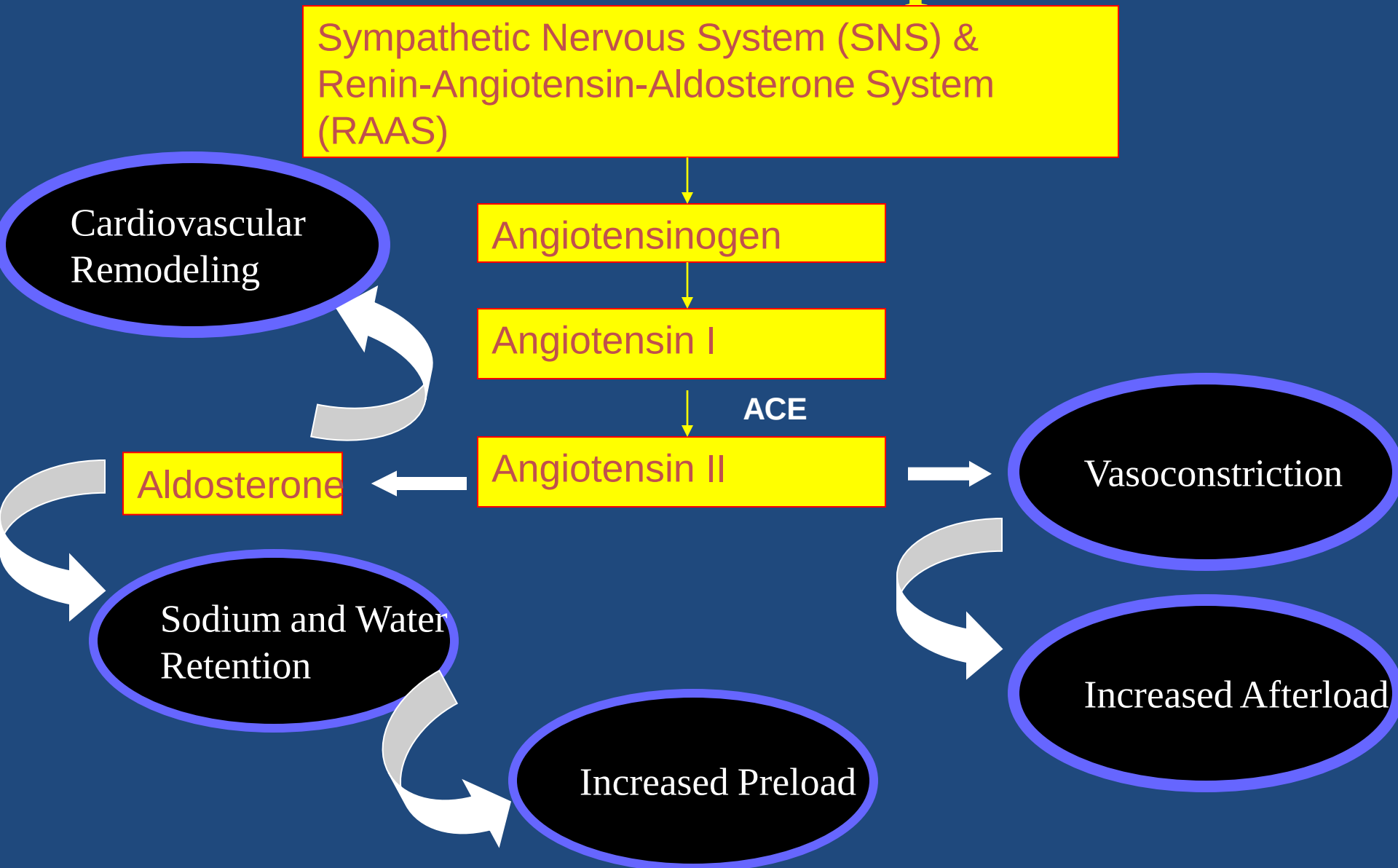
- Cardiologist's understanding of cardiovascular physiology and hemodynamics has only been recently introduced to this field and the care of patients with venous disease.

- Observations made by cardiologists treating patients with leg edema and CVI, has lead to a new understanding of the systemic effects of CVI, and its treatment, particularly in patients with CHF and HTN.

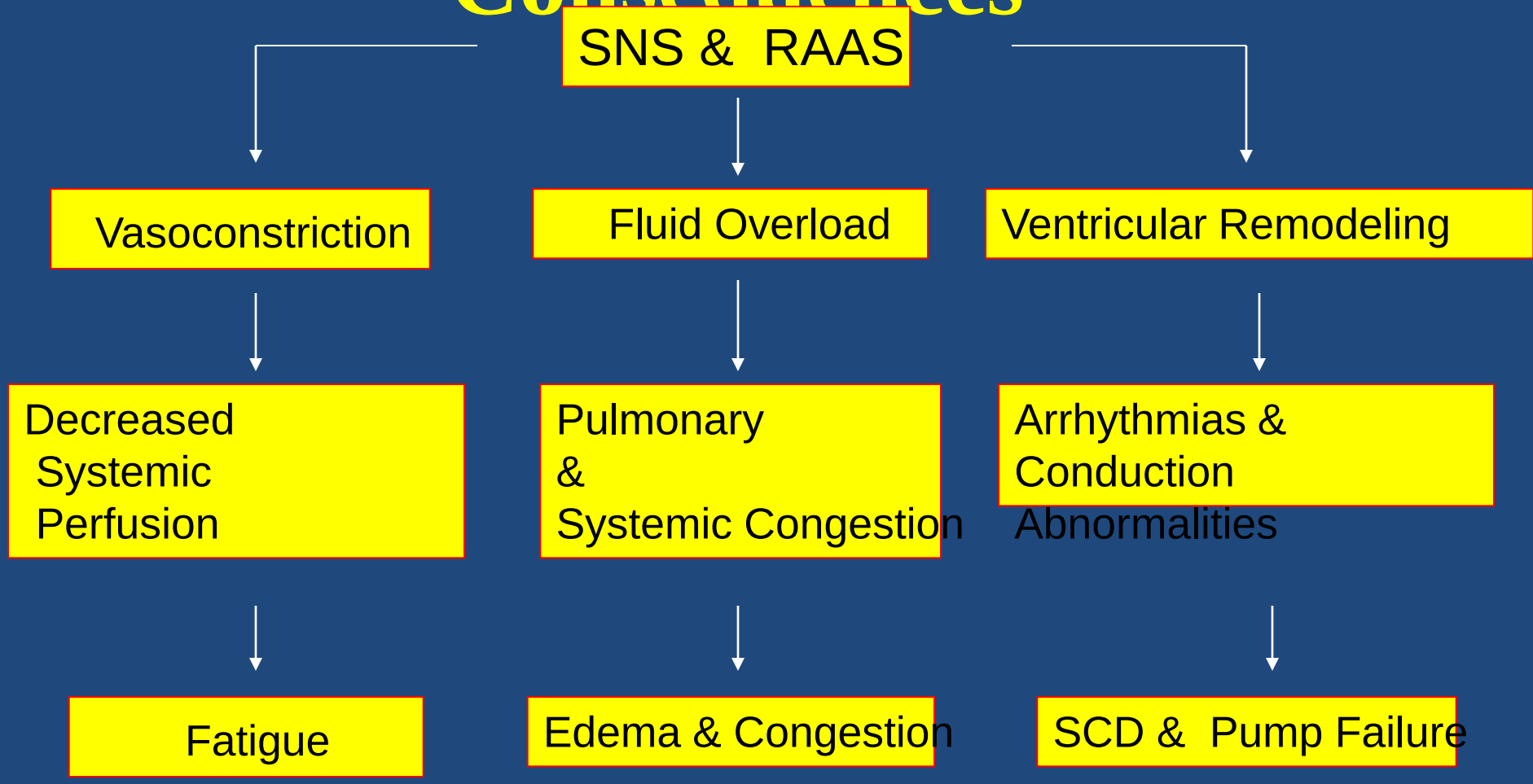
The Observations

- Some patients with CVI and bilateral leg edema who have reflux disease ONLY in one leg and are successfully treated with closure of the refluxing vein, experience disappearance of the swelling not only of the treated leg, but also the untreated leg and require less antihypertensive medications and diuretics!
- Some patients with bilateral leg edema and bilateral reflux disease, do not improve when only one of the refluxing legs is treated. Only after treatment of both refluxing legs, the edema disappears.

Heart Failure: Neurohormonal Response



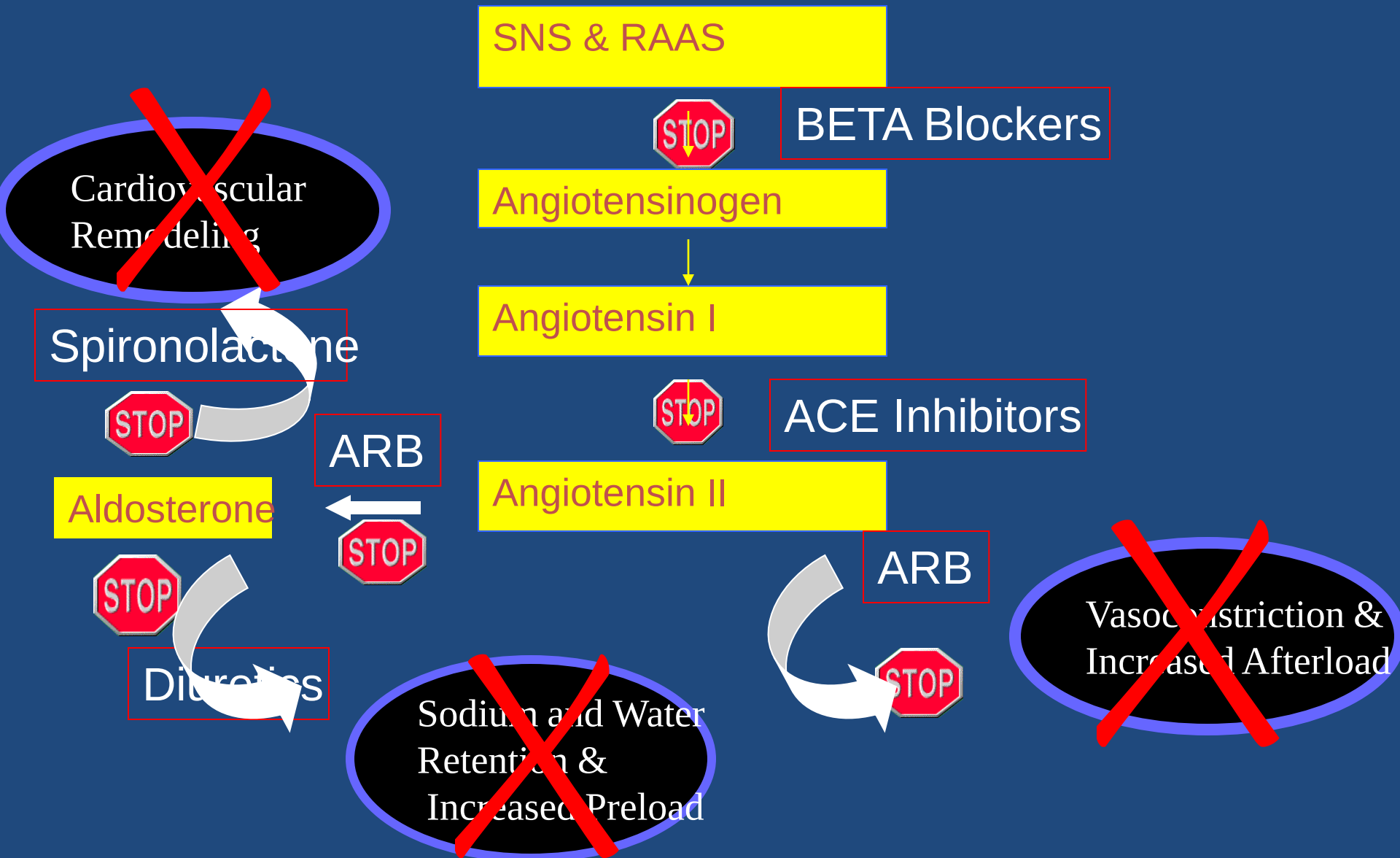
Neurohormonal Activation Consequences



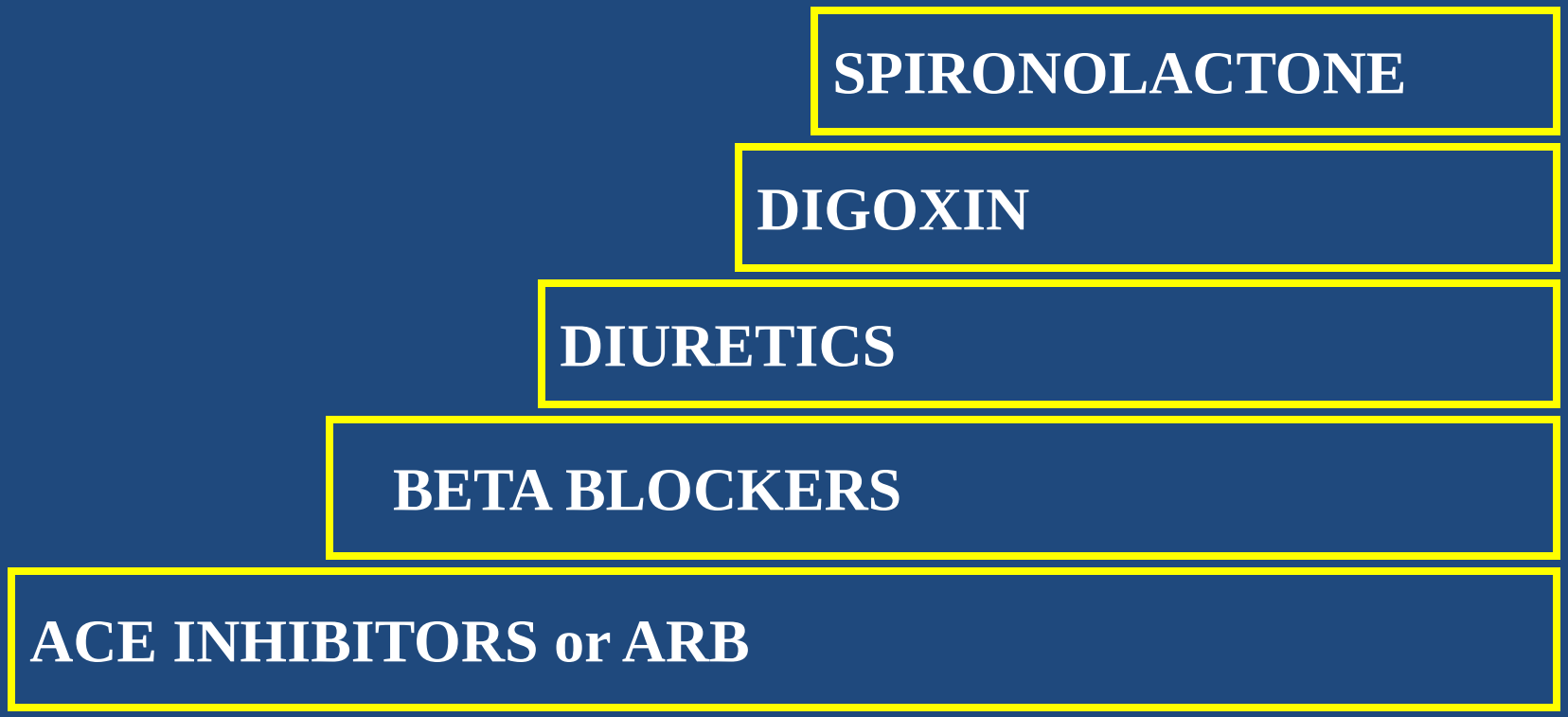
Heart Failure: Pharmaceutical Therapy

- The focus of medical therapy is on blocking neurohormonal compensatory mechanisms that lead to ventricular remodeling and progression of heart failure:
  - Sympathetic nervous system (SNS)
  - Renin-angiotensin-aldosterone system (RAAS)

Neurohormonal Antagonist



OPT: Optimal Pharmacologic Therapy

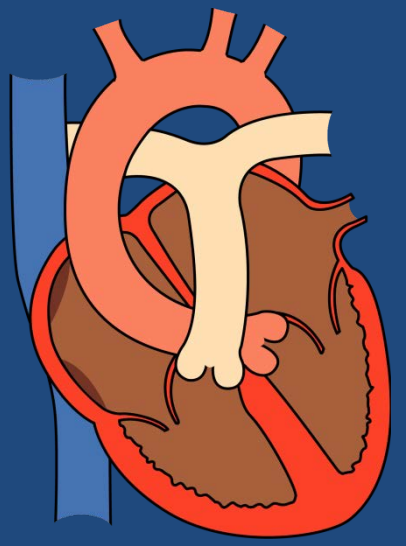


*ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult. 2001; 1-56.

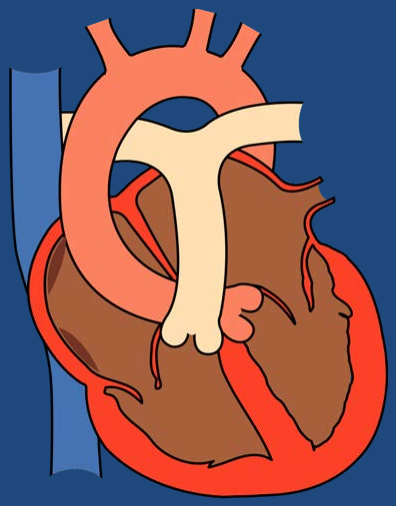
Ventricular Remodeling

- A change in the structure and function of the ventricle in response to injury

- Components:
  - Ventricular dilation
  - Myocyte hypertrophy
  - Interstitial fibrosis
  - Apoptosis
  - Beta receptor down-regulation



Normal



Dilated

The opportunity

- Now that we have a very effective, safe and easy treatment for CVI/venous reflux disease, we ought to study the systemic effects of this disease, and it’s treatment, on cardiovascular system

Chronic Venous Insufficiency (CVI)

THE MISSING LINK

Hooman Madyoon, MD, FACP, FACC

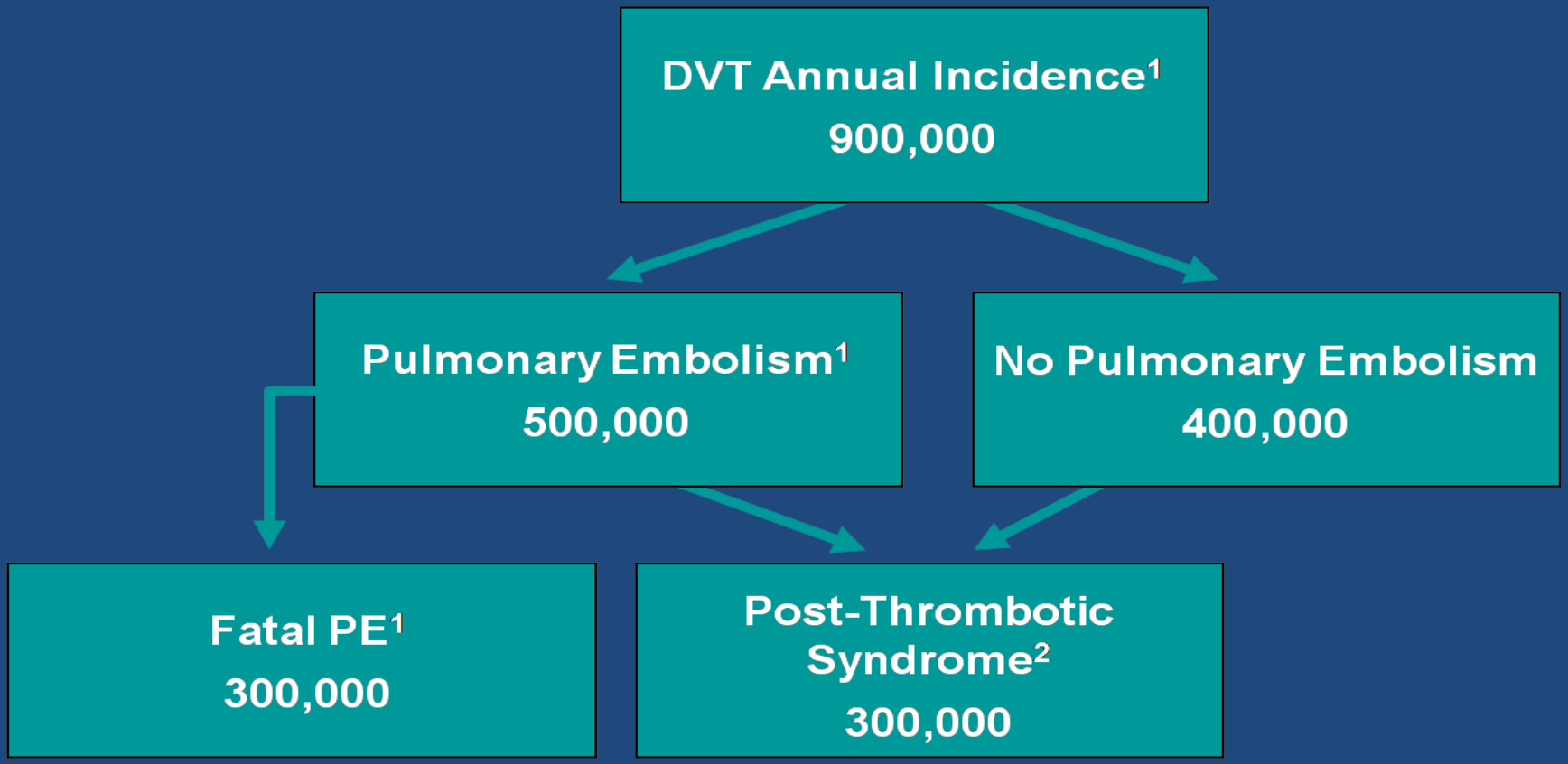
DVT - "A National Crisis…"

- U.S. Surgeon General, 2008

- >600,000 Americans are diagnosed with DVT annually[1]
- 300,000 will develop Post Thrombotic Syndrome (PTS)[2,4]
- 120,000 will suffer recurrent VTE (DVT/PE)[3]
- VTE is the leading cause of preventable hospital death[5] (DVT and PE)
- DVT is the third most common CV Disease[4]
- U.S. spends $2.4B to Treat DVT annually[2]

1. Heit, JA. Venous Thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 2005; 3:1611-17
2. Sharafuddin, M. et al. Endovascular Management of Venous Thrombotic and Occlusive Diseases of the Lower Extremities. J Vasc Interv Radiol 2003; 14:405-423
3. Spencer FA et al. Patient Outcomes After Deep Vein Thrombosis and Pulmonary Embolism: The Worcester Venous Thromboembolism Study. Arch Intern Med. 2008; 168: 425-430
4. Arko F et al. Aggressive Percutaneous Mechanical Thrombectomy of Deep Vein Thrombosis. Arch Surg. 2007;142:513-519
5. National Quality Forum."National Voluntary Consensus Standards for Prevention and Care of Venous Thromboembolism: Policy, Preferred Practices, and Initial Performance Measures." 2008

Annual Incidence of VTE (# of Patients)

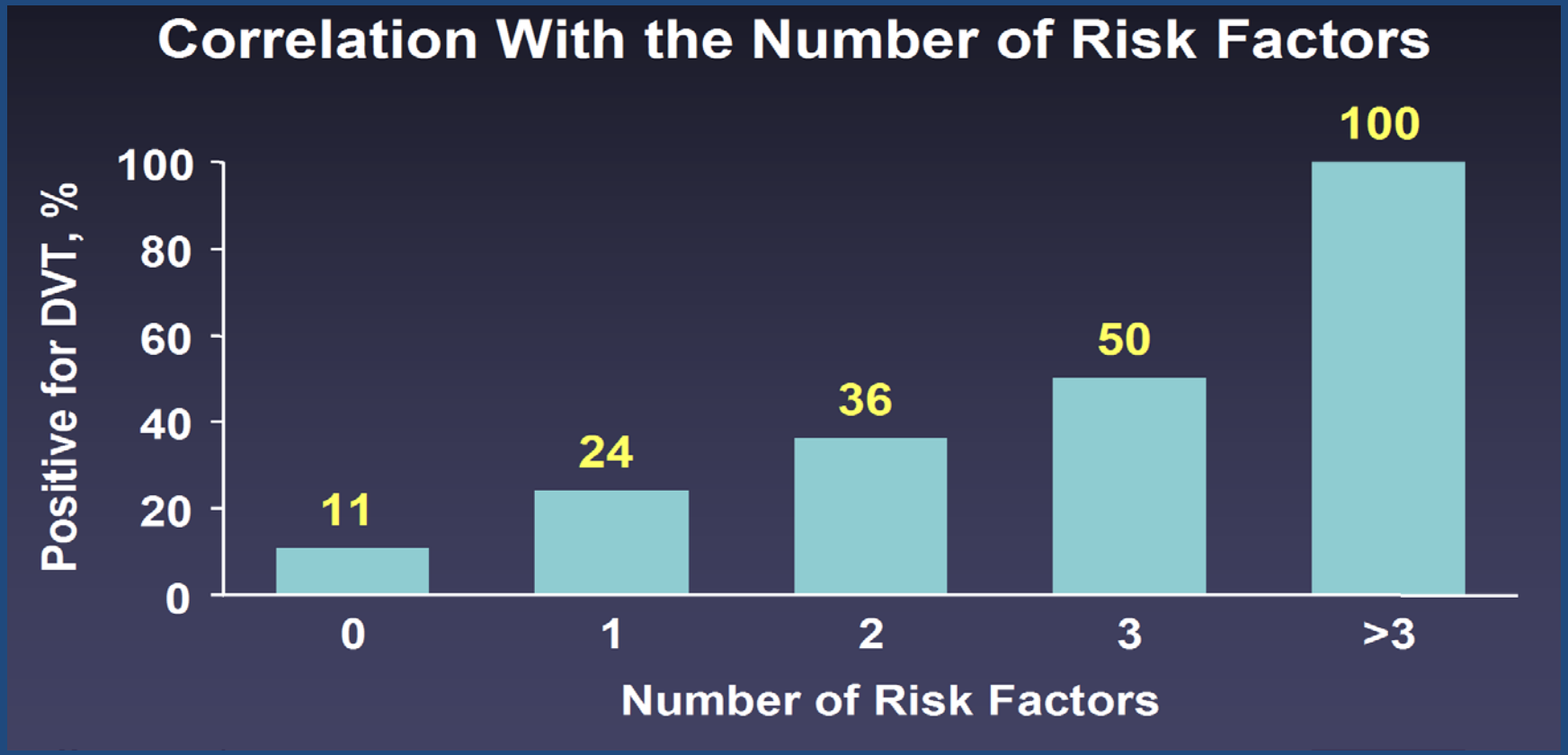


1. Heit, JA. Venous Thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 2005; 3:1611-17
2. Sharafuddin, Melhem, et al. Endovascular Management of Venous Thrombotic and Occlusive Diseases of the Lower Extremities. J Vasc Interv Radiol 2003; 14:405-423

Rising VTE Incidence in Hospitalized Patients

Reprinted with permission from Stein PD, et al. Am J Cardiol. 2005;95:1525-1526.

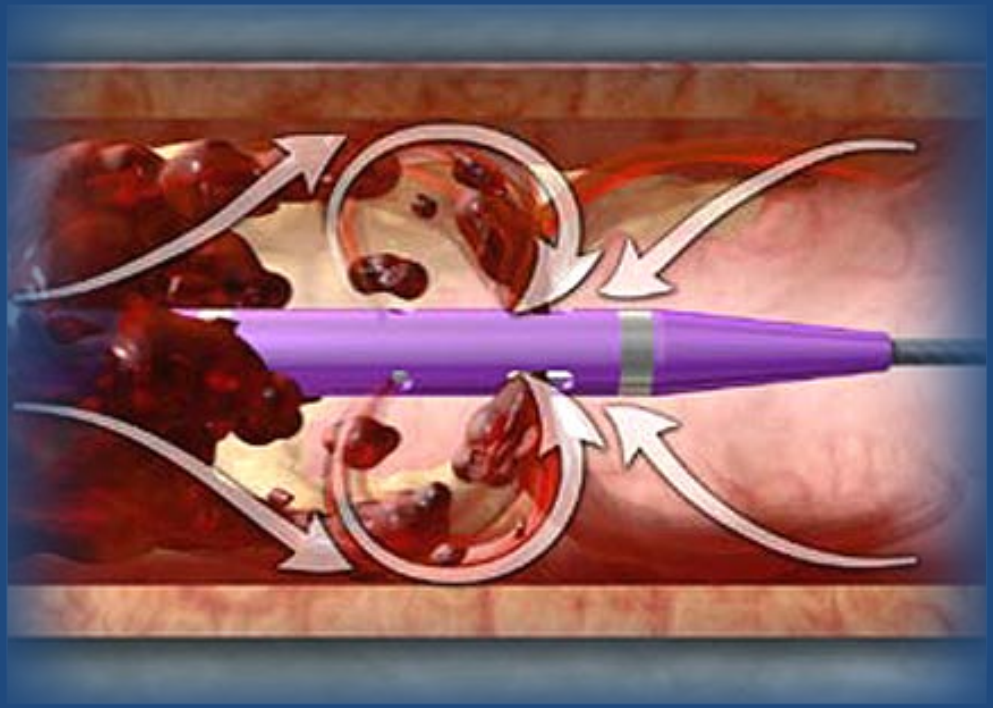
Incidence of DVT in Medical and Surgical Patients



Reprinted with permission from Anderson FA Jr and Spencer FA. Circulation . 2003;107(23 suppl 1):I-9–I-16.

PAO: Therapies

Mechanical Thrombectomy Device (MTD)

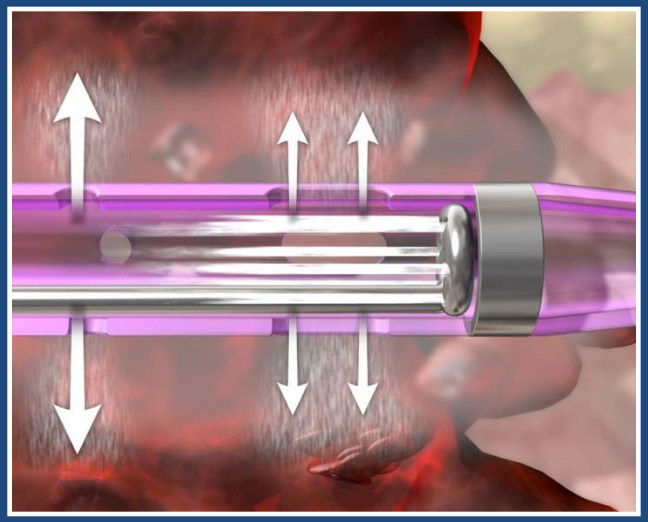


AngioJet® Thrombectomy System

- **Emerging treatment option that allows mechanical removal of thrombus**
- **Powerful saline jets create a low pressure zone around the catheter tip that causes a vacuum effect. Thrombus is drawn into the catheter, where it is fragmented by the jets and then removed from the body**

Power Pulse® Delivery

Mechanism of Action



Inflow remains occluded

Outflow lumen occluded

PSF pulsed through distal windows

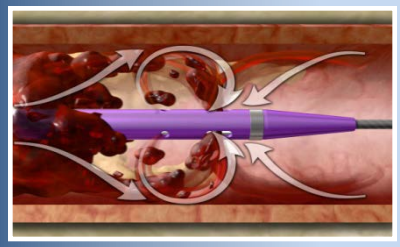
PSF delivered directly into thrombus

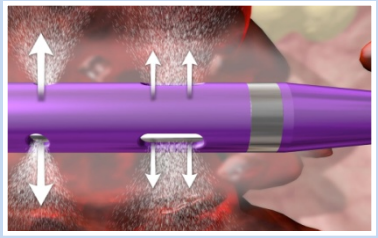
Treatment Approaches

- After access is gained
- Assess initial angiographic images
- Determine treatment approach

Treatment Option 1

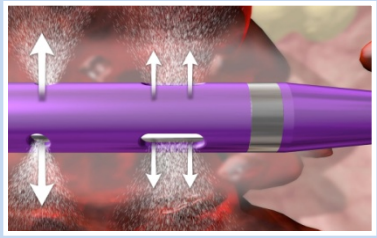
AngioJet Thrombectomy followed by Power Pulse® Delivery option

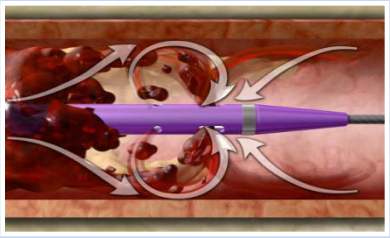




Treatment Option 2

Power Pulse Delivery followed by AngioJet Thrombectomy





Treatment approach is at physician's discretion.

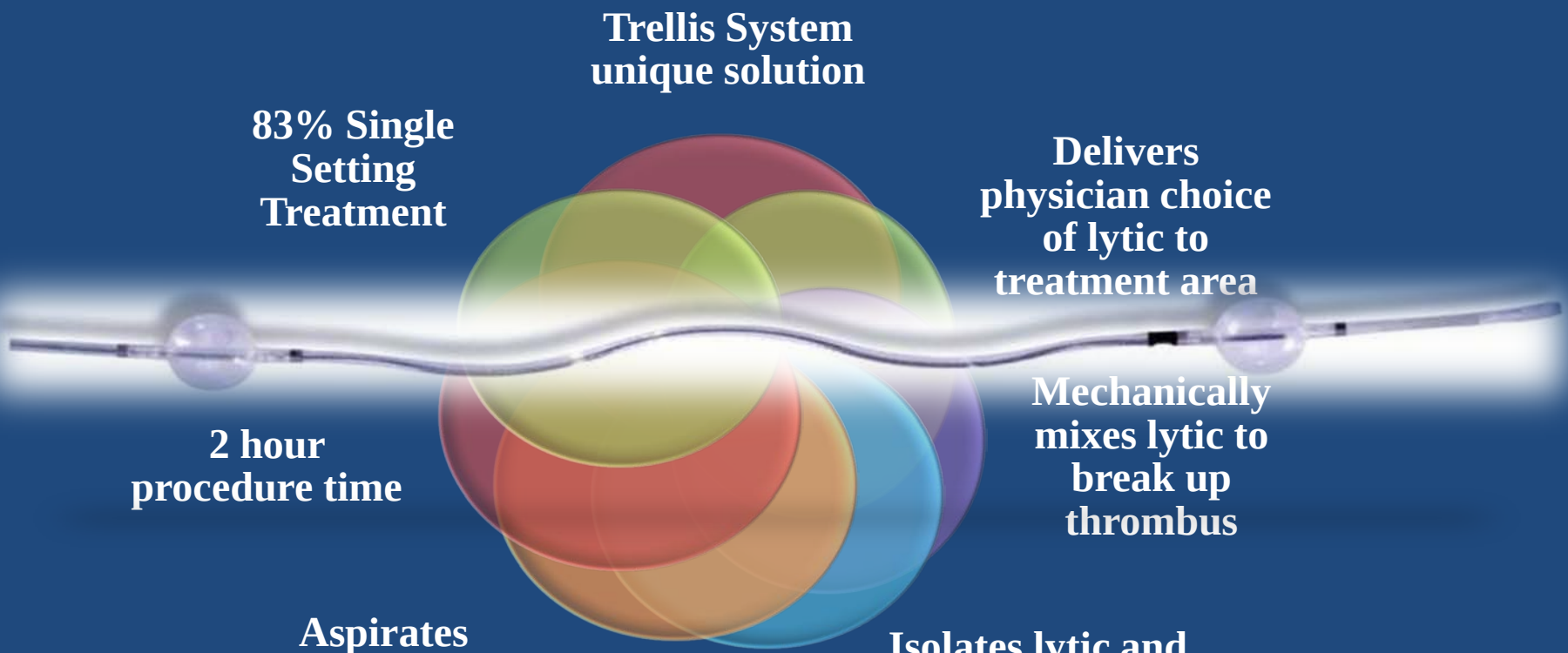
Systemic Thrombolysis vs AC

- Patients who had undergone thrombolysis routinely report better physical functioning and fewer post-thrombotic syndrome
- 85% of patients would undergo thrombolysis over anticoagulation alone if offered the opportunity
- 80% of patients state they are very satisfied with results of thrombolysis
- 33% of patients who are on anticoagulation alone are very satisfied with their results
- (catheter directed lysis registry)

Isolated Thrombolysis Catheter Designed for Single-Setting Treatment of Thrombosis

- Advantages
  - Designed for **Single-Setting** Treatment of DVT
    - Can be done on outpatient basis
    - If patient is already anticoagulated, does not need to be reversed
  - Isolated Thrombolysis
    - TPA is confined to area of treatment
    - Risk of systemic TPA is nullified
  - Quick relief of patient symptoms
  - Prevent Post thrombotic syndrome
  - Decrease amount of time patient may need to be on coumadin

Isolated Pharmacomechanical Thrombolysis Treatment

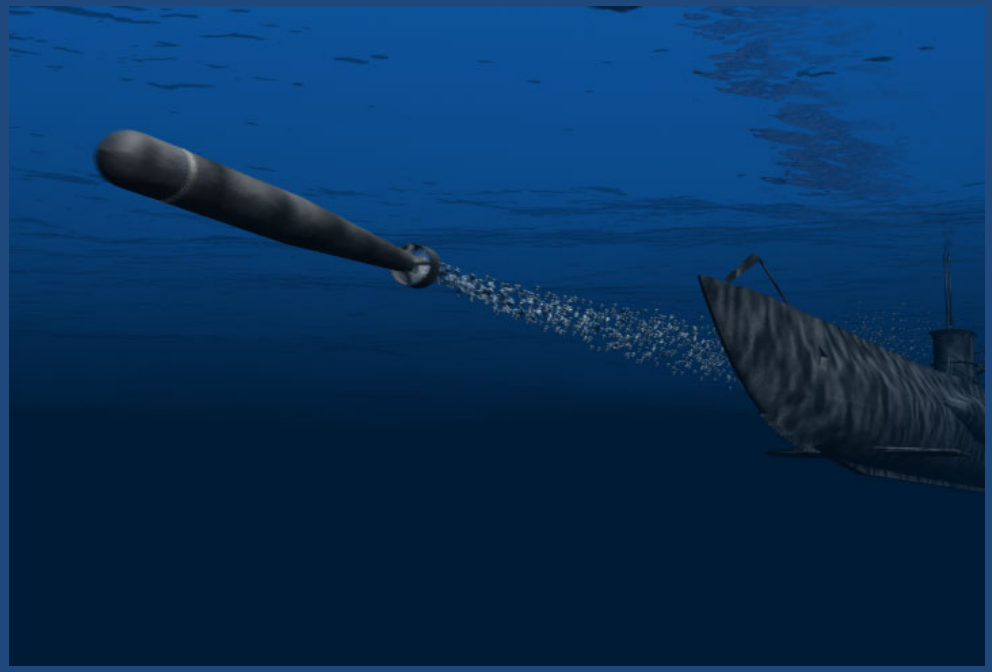


Hematology's viewpoint

- Hematology Today, 6/25/2010
  - Article by *Gregory M. Vercellotti, MD, HemOnc Today Vascular Disorders Section Editor.*
    - *26-43% of patients with DVT get post thrombotic syndrome*
    - *This occurs despite the use of anticoagulation*
    - *"Open vein hypothesis"*
      - *Does early clot removal preserve the valves and prevent PTS?*
      - *There have been many small to moderate sized studies that show that thrombolysis/thrombectomy lowers the rate of PTS*
      - *Problem has been getting patients enrolled in anticoagulation arm*

TORPEDO TRIAL

Thrombus **O**bliteration by **R**apid **P**ercutaneous **E**ndovenous Intervention in **D**eep Venous **O**cclusion “TORPEDO” trial : Mid –Term results



First Randomized Prospective Trial of Patients with acute symptomatic proximal DVT

Percutaneous Endovenous Intervention Reduces Recurrent Venous Thromboembolic Disease and Post-Thrombotic Syndrome in Acute Proximal Deep Venous Thrombosis

TOTAL OUTCOME

	PEVI Group n= 88	**Control Group n= 81**	**p value**
Total VTE	4(4.5%)	13(16%)	p=0.02
PTS	6(6.8%)	24(29.6%)	P<0.001

Conclusions

PEVI + anticoagulation is superior to anticoagulation alone in:

- Reduction of recurrent VTE
- Reduction of PTS
- Reduction of hospital stay
- Reduction of leg edema
- Reduction of skin induration
- Reduction in duration of parenteral anticoagulants
- Subjective perception of improvement

ATTRACT Trial

- Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis
- Multicenter trial currently being conducted
- Objective-- to determine if the thrombolysis in symptomatic patients with acute DVT reduces the occurrence of the post-thrombotic syndrome during 24 months of follow-up.
- Patients randomly assigned to thrombolysis or coumadin arms
- Having good success enrolling patients, probably because of large number of centers enrolled

Thank You!

Pre-treatment

2 weeks post-Closure

*Individual results may vary

Venous Reflux: A Serious Progressive Disease

Varicose Veins

20 Million

Leg Swelling

2-6 Million

Skin Damage

Skin Ulcers

500K

Increased pain and reduced quality of life

[1]White JV, Ryjewski C. Chronic venous insufficiency. Perspect Vasc Surg Endovasc Ther 2005;17:319-27

[2]Image courtesy of Paul McNeill, MD

[3]Image courtesy of Rajabrata Sarkar, MD

[4]Photo source: missinglink.ucsf.edu/.../stasis_dermatitis.html

[5]Photo source: Amor Khachemoune, Catharine Lisa Kauffman: Management Of Leg Ulcers. *The Internet Journal of Dermatology*. 2002. Volume 1 Number 2.

Venous leg ulcers

Treat the source,
not just the symptom

Chronic Venous Insufficiency (CVI)

A Serious Progressive Condition

Varicose Veins

CEAP 2

Leg Swelling

Skin Damage

CEAP 3 & 4

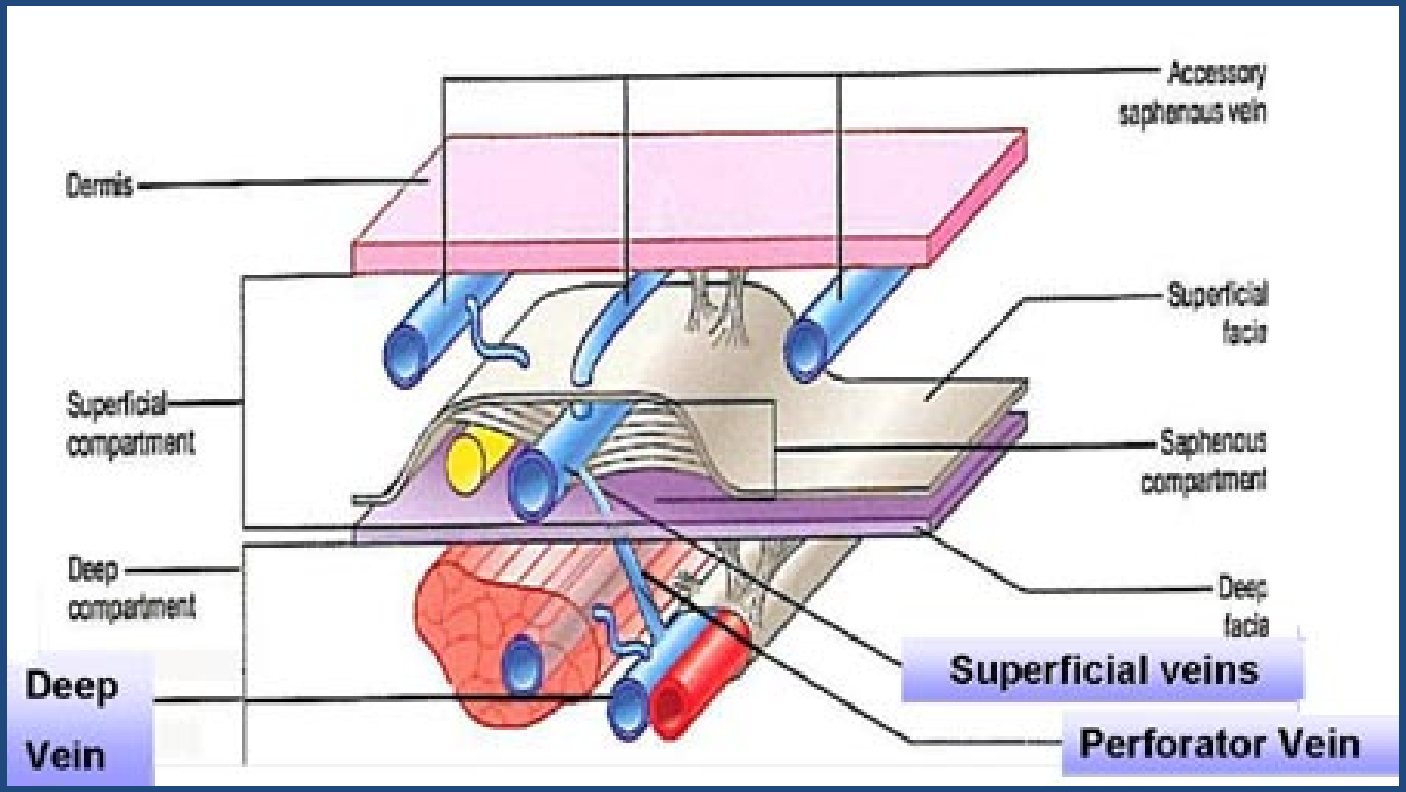
Skin Ulcers

CEAP 6

Increased pain, reduced quality of life

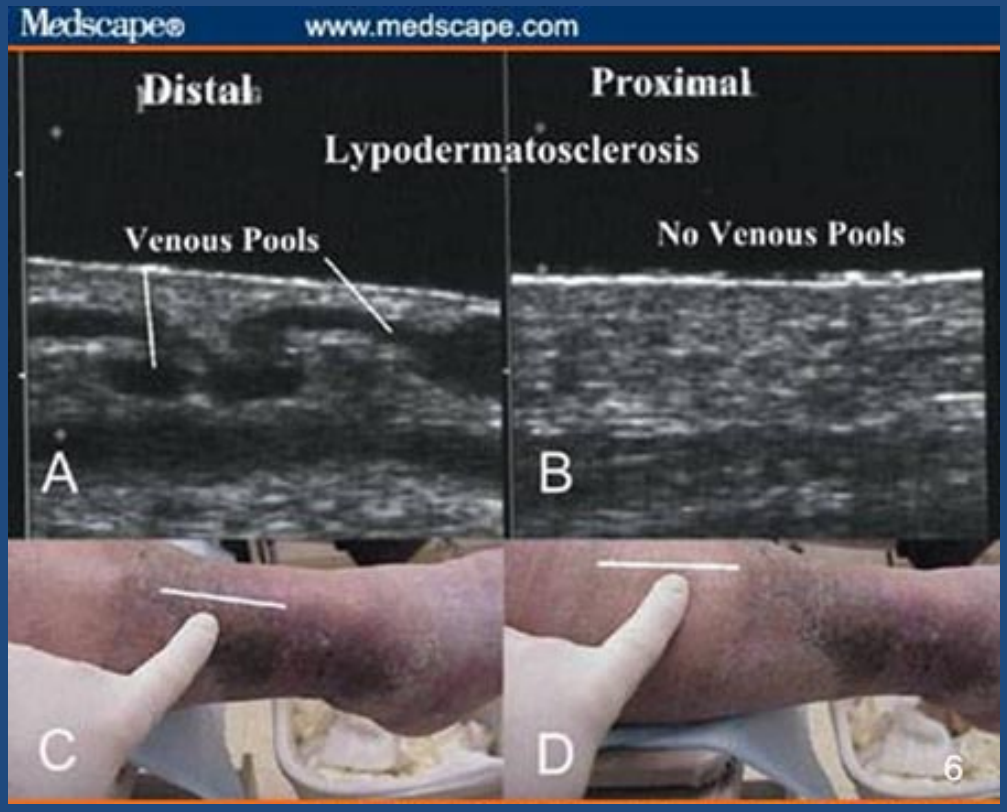
Source & Prevalence of VU Reflux

- Superficial (79%), Perforating (63%), Deep (49.5%)[1]



Tissue Changes Beneath Wound

- Ultrasound images (A, B):
  - Pathologic (C) vs.
  - Non-pathologic (D) areas



Epidemiology of Venous Ulcers

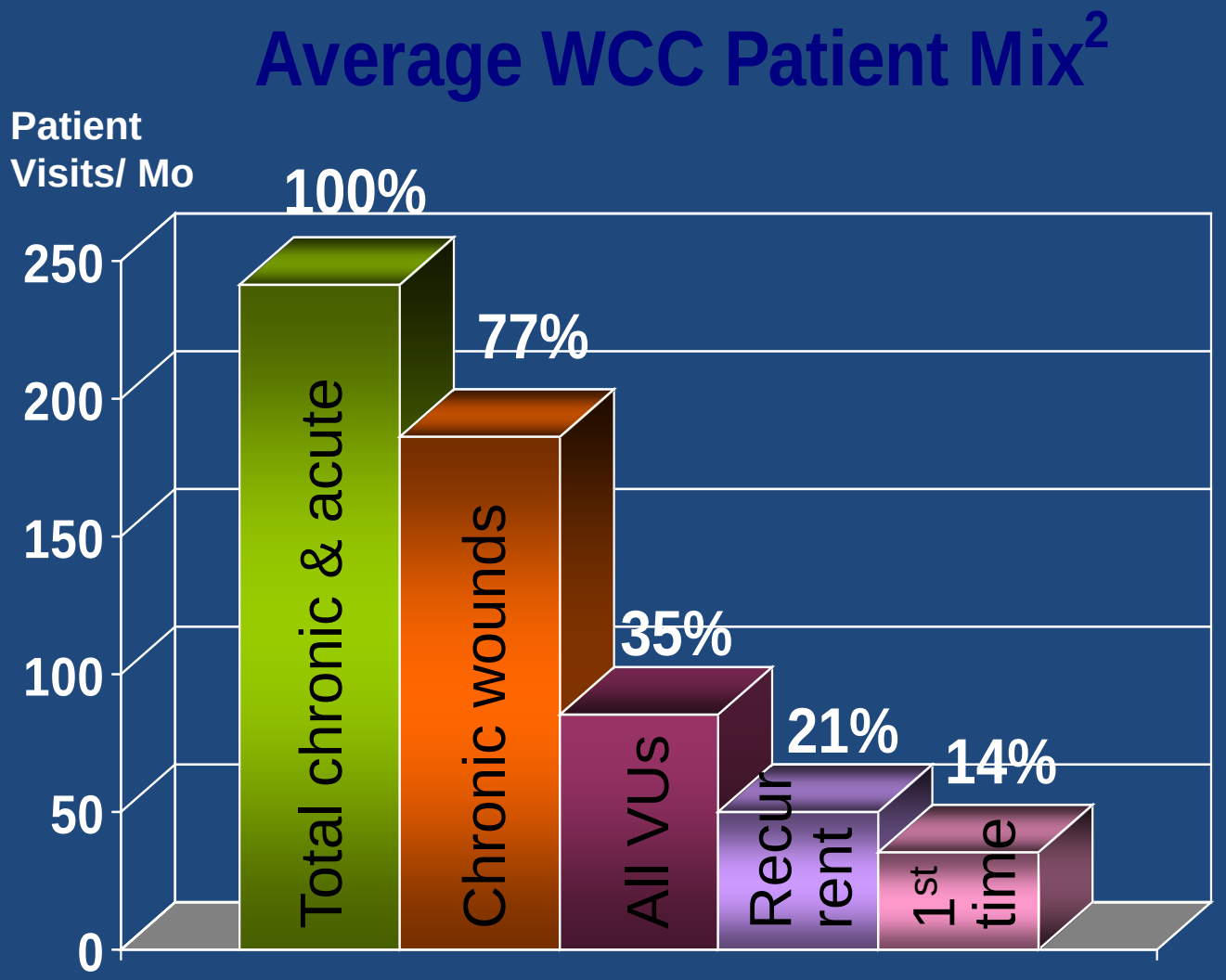
	% Total Population	Affected US Population
Active or Healed VU	0.8%[1]	2.5 Million[1*]
Prevalence	0.29%[1]	870K[1*]
Incidence (1st time ulcer)	18 per[2] 100,000	172K[2*]

Aggressive vein surgery resulted in 46% reduction of VU prevalence from 0.16% in 1988 to 0.09% in Sweden[3]

*Data extrapolated from source

US Wound Care Center (WCC) Patients

- VU is largest patient segment
- VU as % all leg ulcers[1]
  - 50% below knee
  - 70% excluding foot



Current WCC treatment methods

- Conservative treatment is standard of care, even for recurrent or non-healing VUs

Leg Elevation

Unna Boot

Compression Stockings

Apligraf®

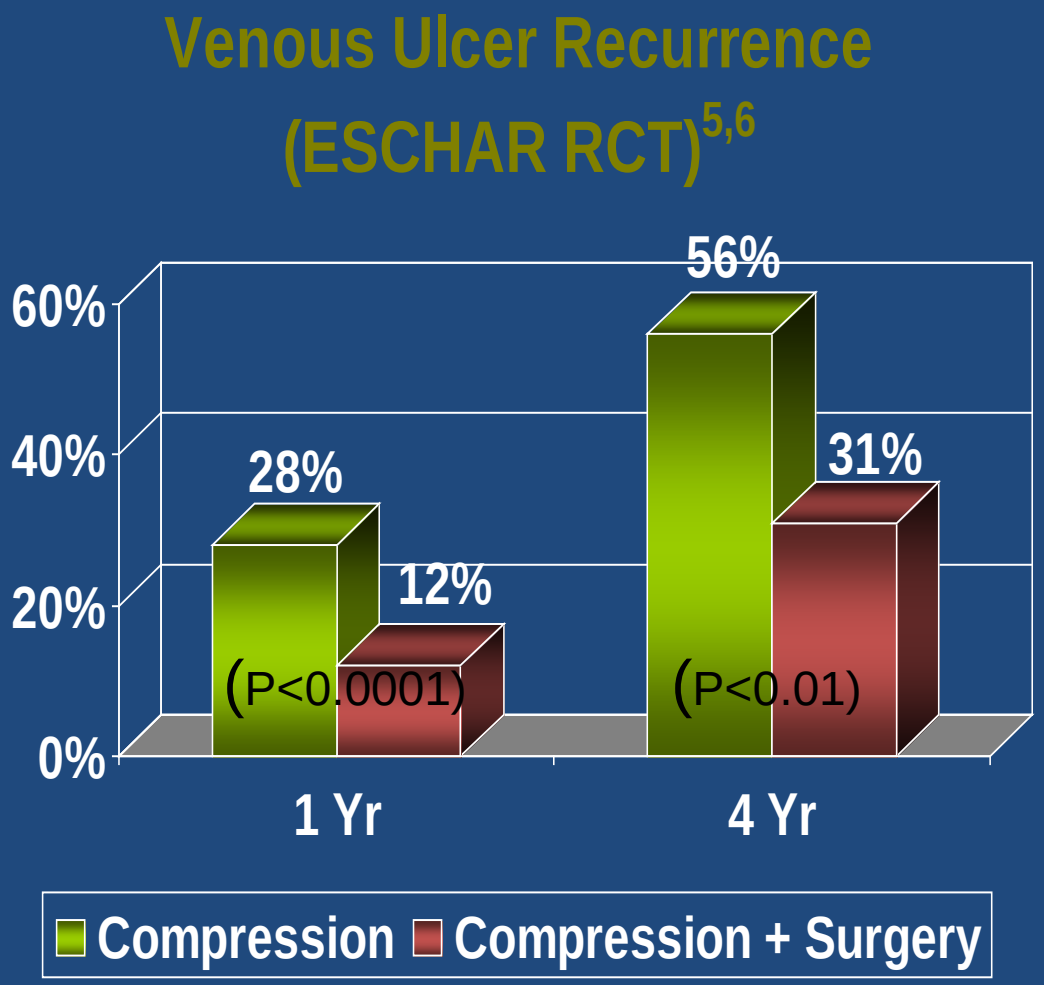
Compression & wound care treat the symptom, not the underlying cause of venous ulcers

Benefits of Conservative Treatment

- Successful at healing VU
  - Mean healing time 5.3 months[3]
  - 40% heal by 3 weeks, 70% heal eventually[4]

Limitations of Conservative Treatment

- Compression + surgery (vein stripping) more effective than compression alone



Consensus Guidelines

Wound Healing Society

- “superficial venous ablation … can be useful in decreasing the recurrence of venous leg ulcers”[9]

American Venous Forum

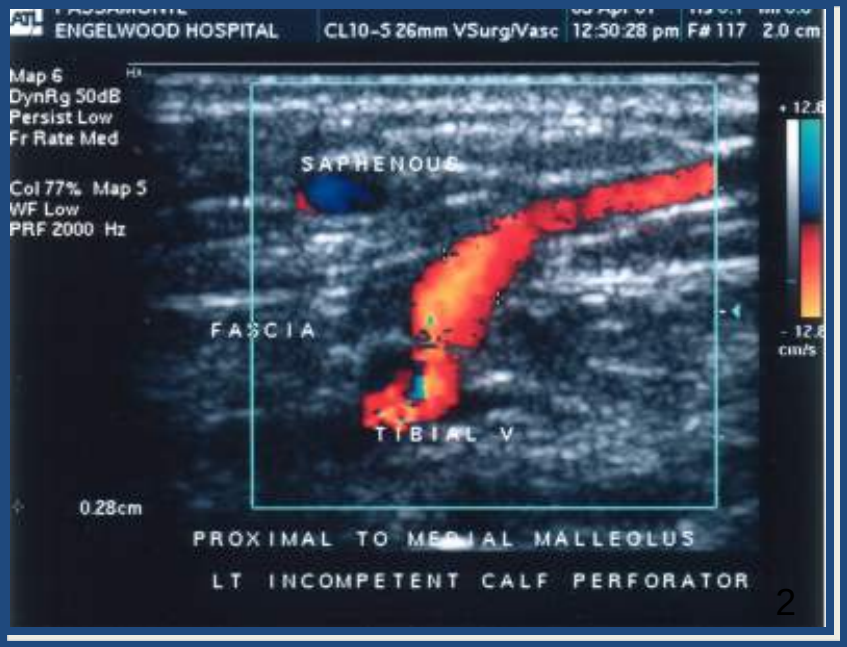
- “We recommend superficial venous surgery to decrease ulcer recurrence in patients with superficial venous reflux”[10]

American College of PHLEBOLOGY

- “Endovenous thermal ablation is the new standard of care”[11]

Insufficiency Diagnosis Criteria

- Reverse flow
  - Superficial system & perforators: ≥ 0.5 sec*
  - Deep system: ≥ 1.0 sec
- Perforator incompetence by diameter at facial level[2]
  - 90% PVs > 3.0 mm
  - 100% PVs > 4.0 mm

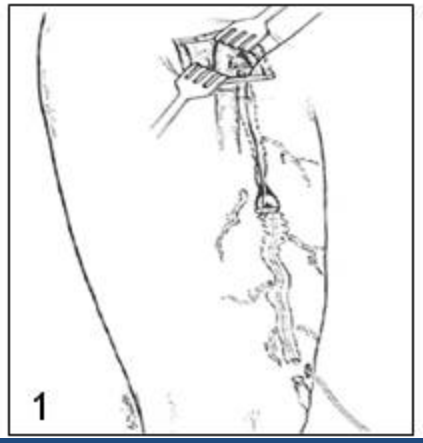


* Note: Some are using >.35 sec as the criteria for clinically significant perforator reflux

Historical Perspective

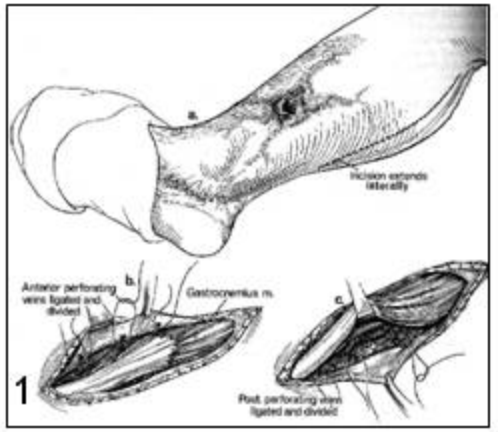
- Little importance on venous disease
  - Traditional treatment: high morbidity
  - Surgeon attitude: surgery last resort
    - Not inclined to perform

Stripping



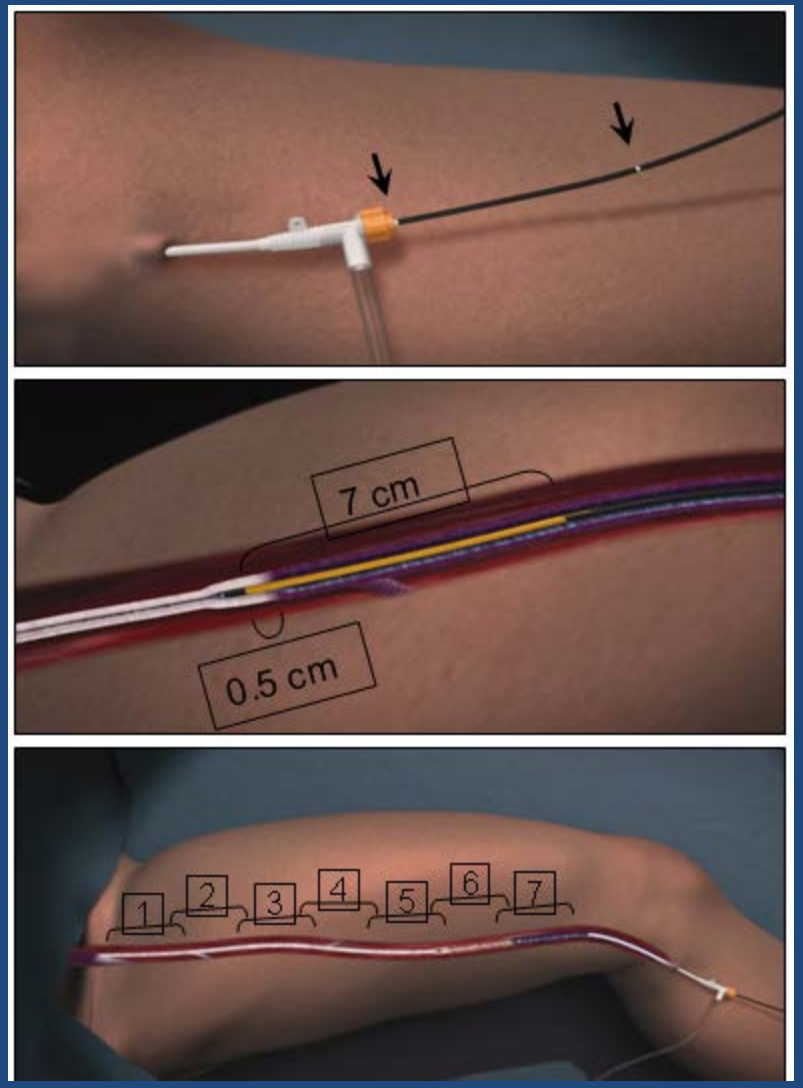
SEPS

Linton



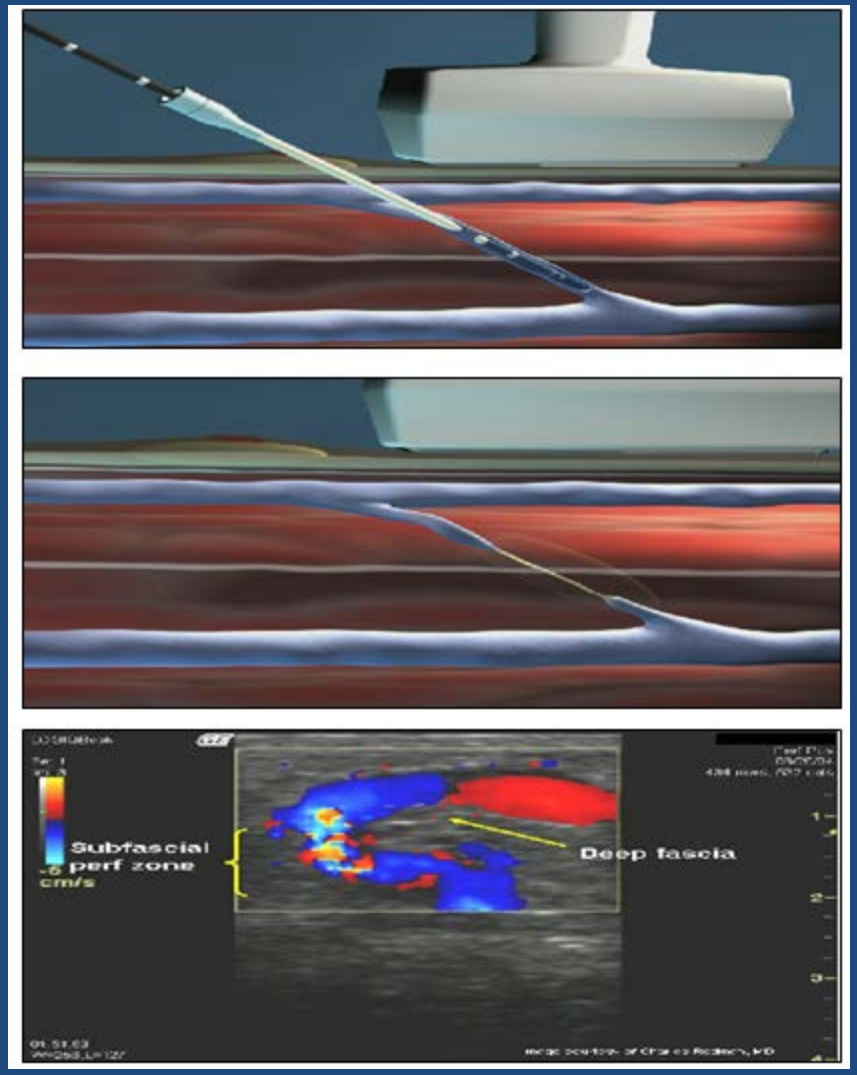
Closure*FAST*™ *Catheter*
for superficial system reflux

- Percutaneous access under ultrasound guidance
- Stationary, temperature controlled 20 second heating cycles
- Stepwise treatment cycles along length of vein in 3 to 5 minutes



Closure*RFS*™ Stylet
for perforating vein reflux

- Percutaneous access under ultrasound guidance
- Temperature controlled 90°C heating at or below deep fascia
- Only endovenous ablation method specifically cleared by FDA to treat incompetent perforator veins




Failed Medical Management

Don’t Wait For This To Happen...

AngioJet® Power Pulse® Delivery Kit In-Service

For use with: AngioJet Xpeedior® 120

DVX Catheters

Solent Proxi

Solent Omni

Please refer to IFU for full prescribing information