Ileo Femoral DVT

"Review and Update"

Ammar Safar, MD, FSCAI, FACC, FACP, RPVI

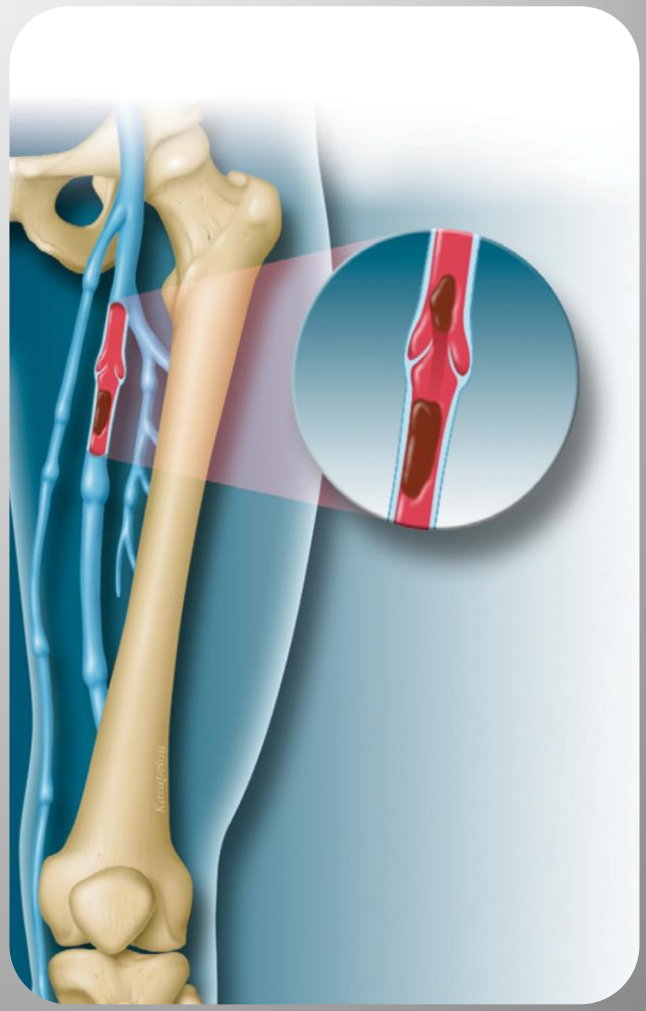
Interventional Cardiology & Endovascular Medicine

Deep Vein Thrombosis

Venous thromboembolism is a major national health problem, with an overall incidence of more than 1 per 1,000 annually.

Deep Vein Thrombosis (DVT) is a potentially life-threatening pathology that can lead to pulmonary embolism (PE), and/or post-thrombotic syndrome (PTS).

The spectrum of DVT to pulmonary embolism can be referred to as venous thromboembolic disease (VTE).



http://www.acep.org/Clinical---Practice-Management/Focus-On--Emergency-Ultrasound-For-Deep-Vein-Thrombosis. Accessed January 2016.

VTE: A Major Source of Mortality and Morbidity

Over **200,000** deaths per year due to PE annually in the U.S. alone.

More than HIV, MVAs & Breast Cancer combined

Over **600,000** patients diagnosed with DVT annually in the US alone

10% of Hospital Deaths most common preventable death

Huge Costs and Morbidity

Recurrence of DVT, post-thrombotic syndrome and chronic PE / PAH are long term sequelae

Some Causes of Death in the US	Annual Number of Deaths
PE	Up to 200,000
AIDS	16,371
Breast Cancer	40,580

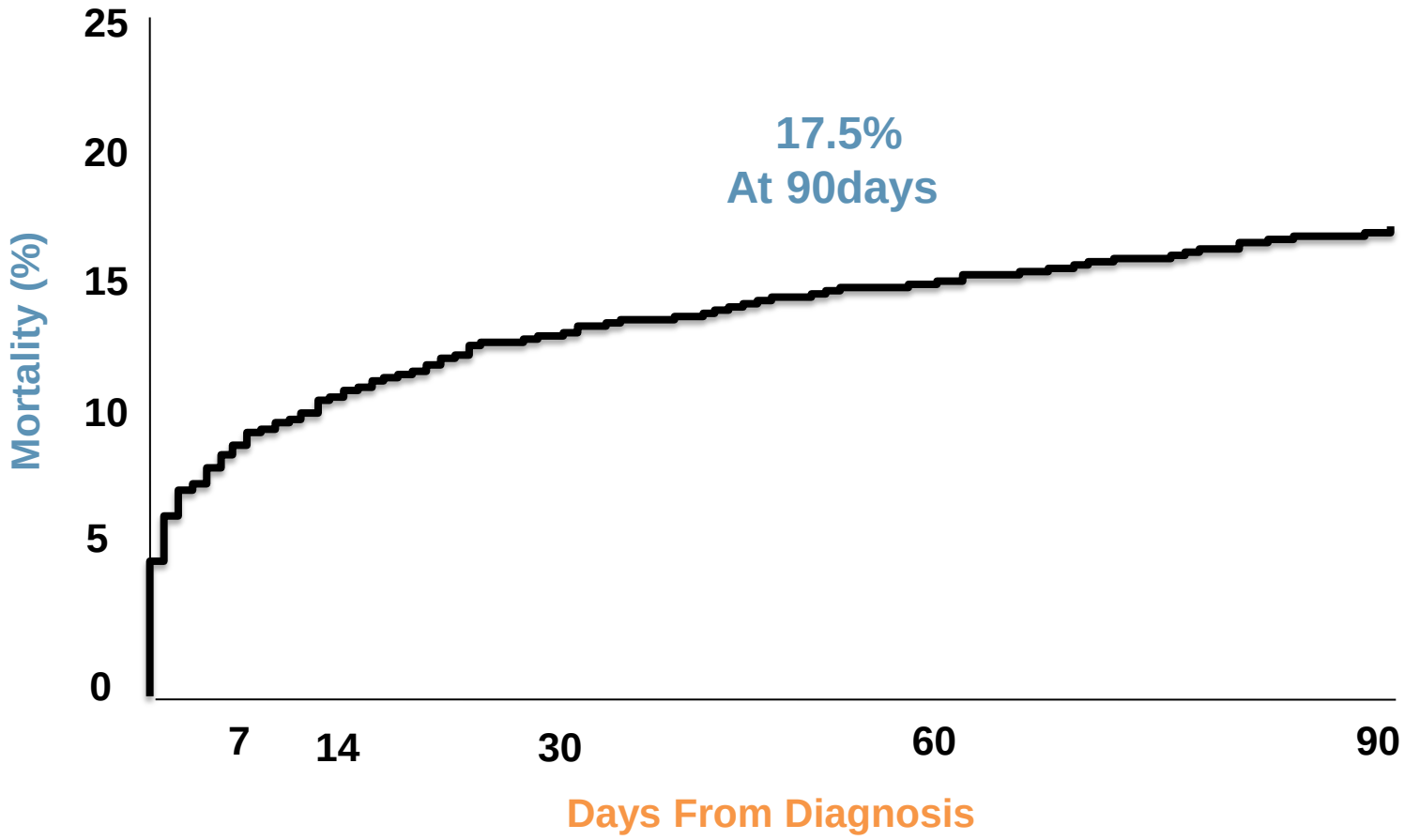
Venous Thromboembolism (VTE) remains a major health problem

In addition to the risk of sudden death

30% of survivors develop recurrent VTE within 10 years

28% of survivors develop venous stasis syndrome within 20 years

Icoper: Cumulative Mortality After Diagnosis of PE



Lancet. 1999;353:1386-1389.

Risk Factors and DVT

Stasis

Age > 40
Immobility
CHF
Stroke
Paralysis
Spinal Cord injury
Hyperviscosity
Polycythemia
Severe COPD
Anesthesia
Obesity
Varicose Veins

Hypercoagulability

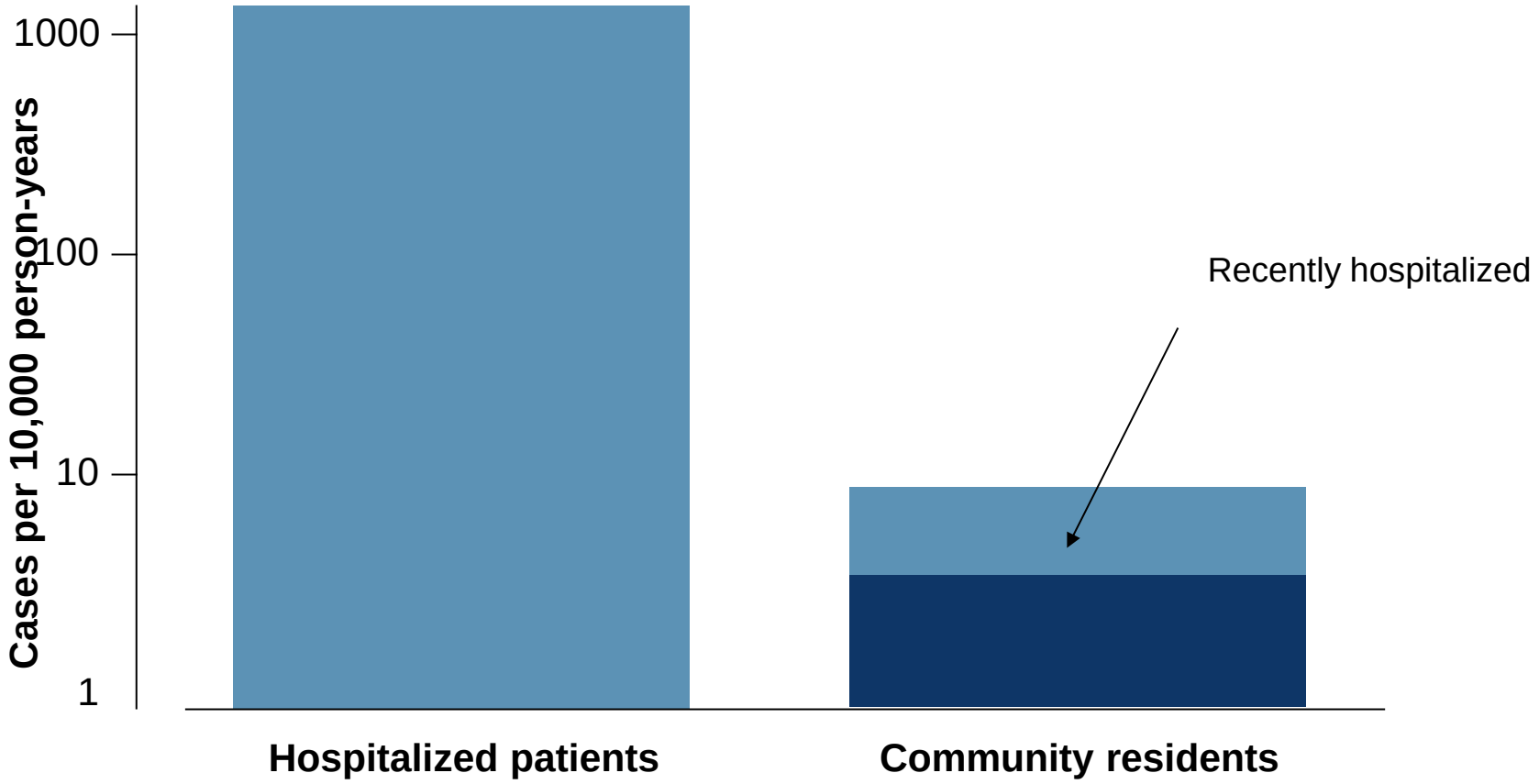
Cancer
High estrogen states
Inflammatory Bowel
Nephrotic Syndrome
Sepsis
Smoking
Pregnancy
Thrombophilia

Endothelial Damage

Surgery
Prior VTE
Central lines
Trauma

Most hospitalized patients have at least one risk factor for DVT

VTE is a Disease of Hospitalized and Recently Hospitalized Patients



Heit – Mayo Clin Proc 2001;76:1102

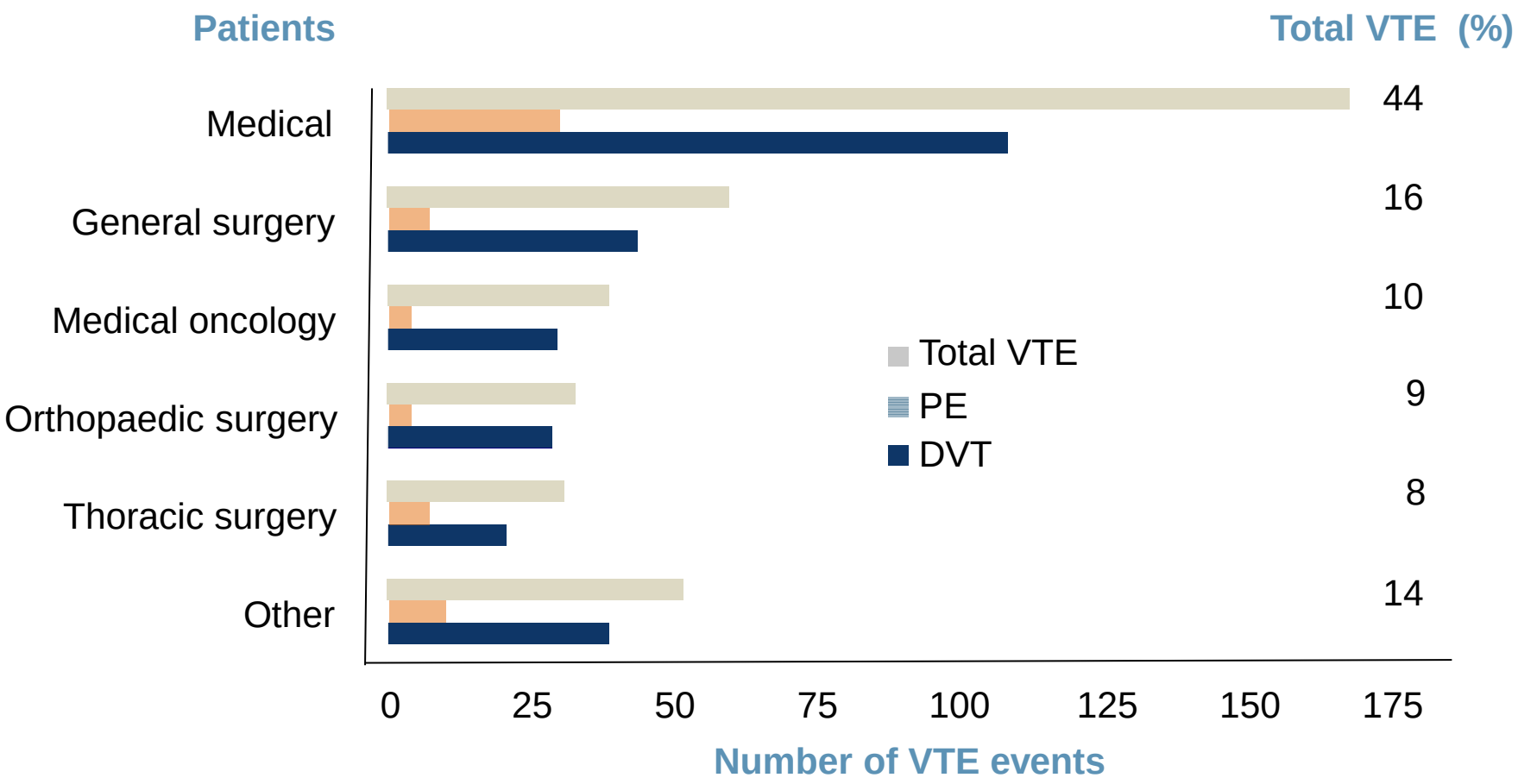
Risk of DVT in Hospitalized Patients

No prophylaxis + routine objective screening for DVT

Patient Group	DVT Incidence
Medical patients	10 - 26 %
Major gyne/urol/gen surgery	15 - 40 %
Neurosurgery	15 - 40 %
Stroke	11 - 75 %
Hip/knee surgery	40 - 60 %
Major trauma	40 - 80 %
Spinal cord injury	60 - 80 %
Critical care patients	15 - 80 %

Heit – Mayo Clin Proc 2001;76:1102

VTE According to Service (N=384)



Goldhaber SZ et al. *Chest* 2000;118:1680-4.

DVT Prophylaxis

DVT risk and prophylaxis in the hospitalized patient

Low Risk	Moderate Risk	High Risk
Ambulatory patient *without* additional VTE Risk Factors	All other patients. Most patients (not LOW or HIGH category)	Elective major lower extremity arthroplasty
Ambulatory patient with expected LOS ≤ 2 days, or same day/minor surgery		Hip, pelvic, or sever lower extremity fractures
Only a few patients!		Acture spinal cord injury with paresis
		Multiple major trauma
		Abdominal or pelvic surgery for cancer
Ambulation and Education	*Px indicated*	*Px indicated*

Physicians at UCSD use these checklists to assess all adult inpatients when they are admitted, transferred between units, or post-op

DVT and Your Cancer Patient

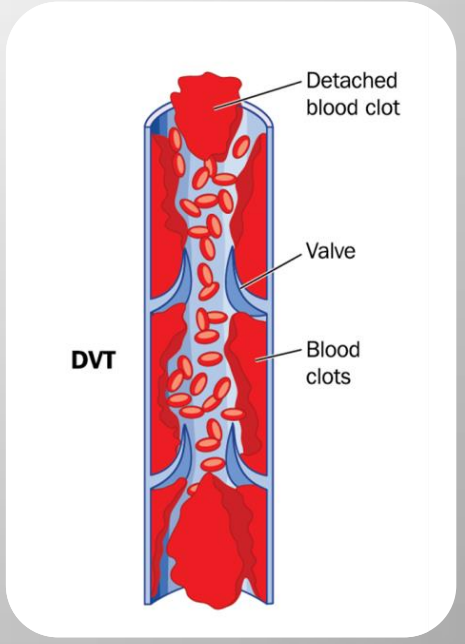
Patients with cancer who develop VTE are at higher risk of both ***recurrence and death*** than other patients with VTE. Because of improved treatment and longer survival, patients with cancer account for an increasing proportion of those with VTE.

- VTE can occur before cancer is evident, at the time of the cancer diagnosis and at any point in the clinical course of patients with known cancer.
- VTE is particularly likely to occur during intensive chemotherapy and as a complication of cancer surgery.
- For years, clinicians have been aware of so-called "warfarin failure"-the tendency to develop recurrent VTE despite an INR between 2.0 and 3.0-in patients with VTE and cancer. Recent clinical trials have shown that **long-term LMWH** in a treatment dose reduces the recurrence rate of VTE in cancer patients by 50% compared with warfarin (INR 2.0-3.0).

Diagnosing DVT

The Challenge - Approximately ***half of patients with DVT are asymptomatic.***

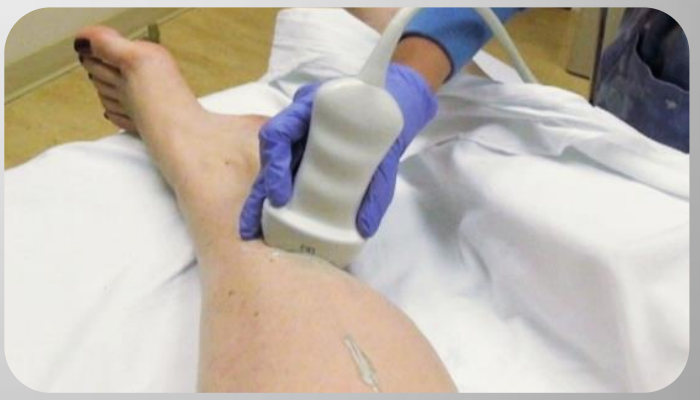
Symptoms of DVT include swelling, pain, tenderness, warmth, and prominent superficial veins on the affected limb.



Patients with suspected DVT frequently present to hospital emergency departments. Since symptoms and signs of DVT can be non-specific and found in a wide variety of non-thrombotic disorders, timely diagnostic testing must be performed to correctly identify patients with VTE.

Diagnosis of DVT

- The gold standard to diagnose DVT and PE remains **Doppler ultrasound** and CT, respectively. D-dimers, V/Q scans, and other modalities may be useful in some scenarios.



However, this range of diagnostic testing options has resulted in wide practice variations.

The Real Question:

What do we do with those patients that develop a DVT? And Why?

GOALS: Decrease the risk of:

1. Recurrence of DVT.
2. Fatal pulmonary embolism (PE)
3. Long term sequelae of DVT

Is current in-hospital treatment adequate?

Anticoagulation

Compression Stockings

Can we do better for these patients?

Using ***multidisciplinary team*** approach

What are the options for ***thrombus removal***

Offering ***minimally invasive*** solutions

SOX Trial

Elastic Compression Stockings vs Placebo Control

Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Susan R Kahn, Stan Shapiro, Philip S Wells, Marc A Rodger, Michael J Kovacs, David R Anderson, Vicky Tagalakis, Adrielle H Houweling, Thierry Ducruet, Christina Holcroft, Mira Johri, Susan Solymoss, Marie-José Miron, Erik Yeo, Reginald Smith, Sam Schulman, Jeannine Kassis, Clive Kearon, Isabelle Chagnon, Turnly Wong, Christine Demers, Rajendar Hanmiah, Scott Kaatz, Rita Selby, Suman Rathbun, Sylvie Desmarais, Lucie Opatrny, Thomas L Ortel, Jeffrey S Ginsberg, for the SOX trial investigators

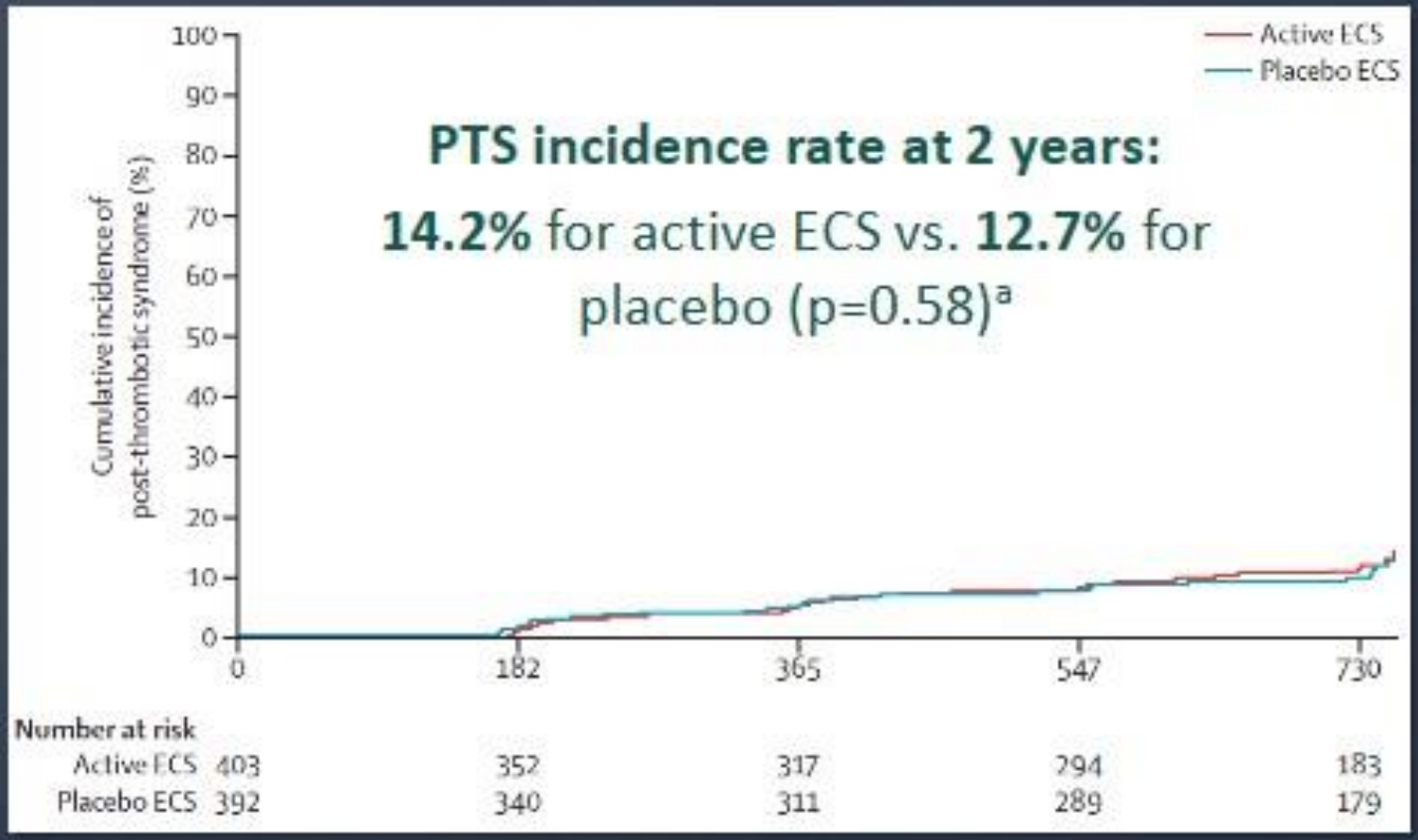
- **Objective:** To evaluate the effectiveness of elastic compression stockings (ECS), compared with placebo stockings to prevent post-thrombotic syndrome (PTS)
- **Design:** Multicenter, randomized, placebo-controlled trial of active (N=410) vs placebo (N=396) ECS
- **Key Inclusion Criteria:** First indicative, proximal DVT (with or without coexisting pulmonary embolism or distal DVT)
- **Primary Endpoint:** PTS diagnosed at 6 months or later using Ginsberg's criteria (ie, leg pain and swelling of ≥1 month)

Kahn SR, Shapiro S, Wells PS, et al SOX trial investigators. Lancet. 2014 Mar 8;383(9920):880-8

SOX Trial Results

Elastic Compression Stockings vs Placebo Control

"ECS did not prevent PTS after a first proximal DVT"



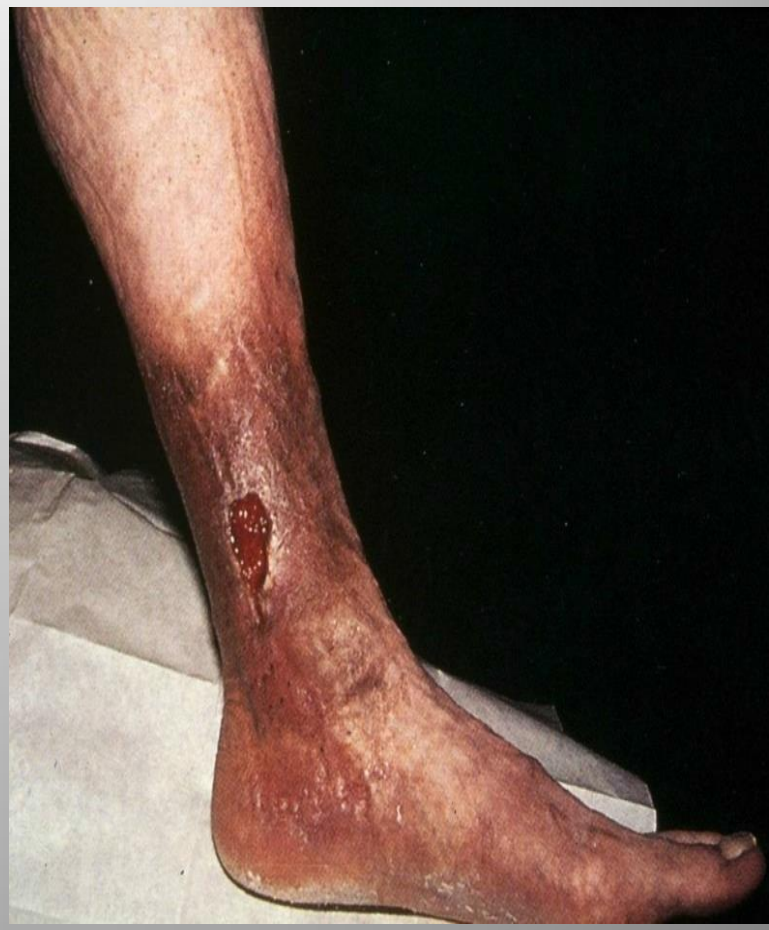
Kahn SR, Shapiro S, Wells PS, et al SOX trial investigators. Lancet. 2014 Mar 8;383(9920):880-8

Post-thrombotic Syndrome (PTS)

- ***Chronic pain, edema*** and fatigue of affected limb after DVT

- Severe PTS may result in venous claudication, stasis dermatitis, ***subdermal fibrosis and ulceration*** -> tissue loss

- ≥40% of patients within 2 years of first lower extremity DVT



https://www.vtematters.co.uk/patient/associated-conditions/~/media/EMS/Conditions/Generics/Brands/Lovenox/Ireland%20-%20United%20Kingdom/PTS.ashx

Post-thrombotic Syndrome (PTS)

- As assessed by Villalta score, more severe PTS is predicted by:
  - Common femoral or iliac DVT (IFDVT)
  - Higher BMI
  - Prior ipsilateral DVT
  - Older age
  - Female gender
- Patients with PTS have overall lower QOL scores and less improvement in symptoms over time with conventional therapy

What is the Villalta Score?

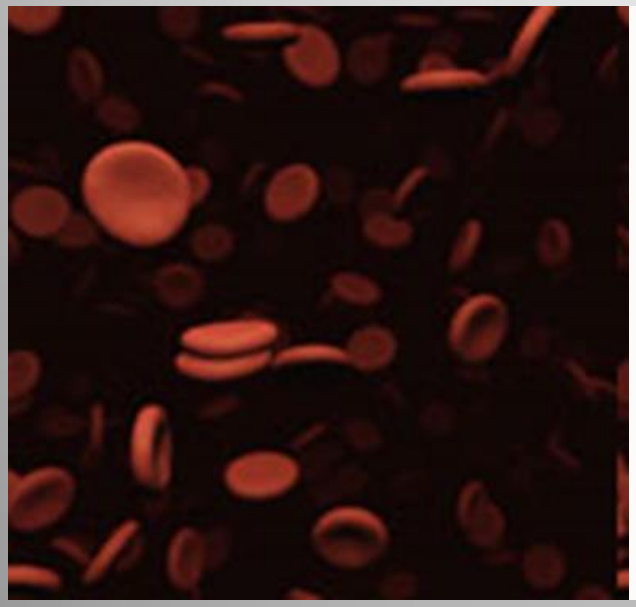
Symptoms	Clinical Signs
Pain	Edema
Cramps	Skin induration
Heaviness	Hyperpigmentation
Pruritus	Redness
Paraesthesia	Pain during calf compression
	Venous ectasia
Each symptom is rated as: 0 (absent), 1 (mild), 2 (moderate), or 3 (severe)	

Scoring	
No PTS	0–4
Mild	5–9
Moderate	9–14
Severe	15+

Villalta Score is the only validated measure for PTS.

1. Villalta S, Bagatella P, Piccioli A, et al. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome Haemostasis 1994;24:158a.
2. The Villalta PTS scale (sometimes called the Villalta-Prandoni scale) has been adopted by the International Society on Thrombosis and Haemostasis (ISTH) as a standard to diagnose and grade the severity of PTS in clinical studies: Kahn, Sr (2016).
3. Guidance for the prevention and treatment of the post-thrombotic syndrome. J Thromb Thrombolysis 2016; 41: 144–153.

Medical management is inadequate for *many VTE patients*



Anticoagulation therapy

- Does not reduce or eliminate the **existing thrombus**
- Does not prevent long-term **damage to the vein and valves,** leading to high levels of PTS[3,4]
- While it reduces the risk of Pulmonary Embolism, the risk remains significant[5]
- 50% of patients on oral therapy are at sub-therapeutic levels[1,2]

1. Clark, N et al, Thromboembolic Consequences of Subtherapeutic Anticoagulation in Patients Stabilized on Warfarin Therapy: The Low INR Study, Pharmacotherapy 2008; 28(8): 960-967.
2. Pirmohamed, M, Warfarin: almost 60 years old and still causing problems, Br J Clin Pharmacol 62(5): 509-511.
3. Comerota AJ et al. Thrombolysis for iliofemoral deep venous thrombosis. Expert Rev Cardiovasc Ther 2013; 11(12): 1631-1638.
4. Comerota AJ et al. Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. J Vasc Surg 2012; 55:768-73.
5. Kearon C et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. CHEST 2012; 141(2)(Suppl):e419S-e494S.

Benefits of Removing Thrombus

New options to remove thrombus are being utilized for treatment of DVT.

Interventional options can now offer the potential to provide:

Immediate removal of thrombus providing **flow restoration**	Potential to reduce risks of pulmonary embolism	Quick restoration of flow providing symptom relief and **return of valve function**	**Possible** reduction of PTS with early thrombus removal

Interventional treatment offers the option to quickly remove thrombus, which provides flow restoration and rapid symptom relief and the ***potential for decreasing PTS***.

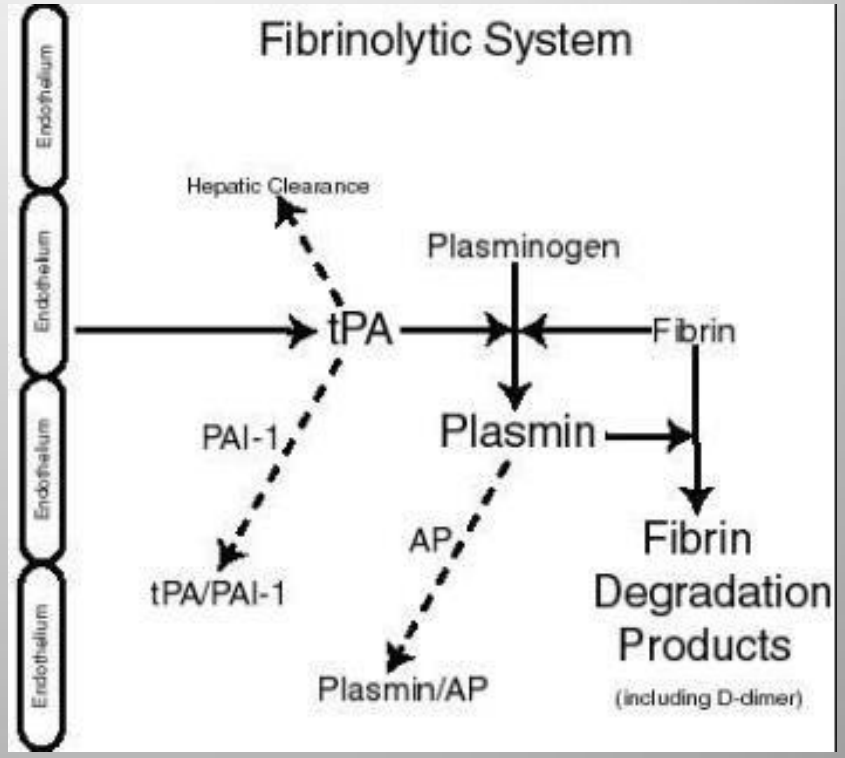
Interventional options in the treatment of DVT

Catheter directed lytic use	Mechanical thrombectomy	Pharmacomechanical thrombus removal	IVC Filters
Used for older thrombus or larger clot burden where thrombolytic is delivered directly to the site of thrombus	Mechanical removal of acute thrombus, to debulk and restore flow	Combination treatment utilizing lytics with mechanical thrombectomy for quicker and improved thrombus removal	Filter designed to capture an embolism; a blood clot that has broken loose

Depending on the age and volume of the thrombus, additional techniques can be employed to remove or dissolve thrombus – assisting the body's natural ability to resolve the clot burden.

Thrombolysis for Acute DVT

- tPA



Mechanical Thrombectomy

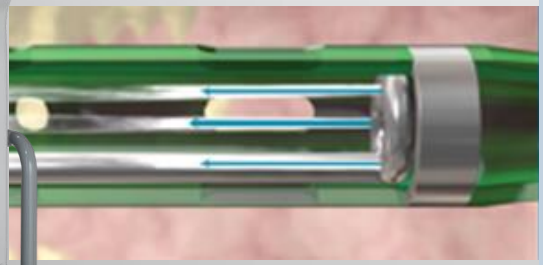
Mechanical thrombectomy is an interventional technique where medication is infused directly into the DVT, and then a device macerates and removes the clot.

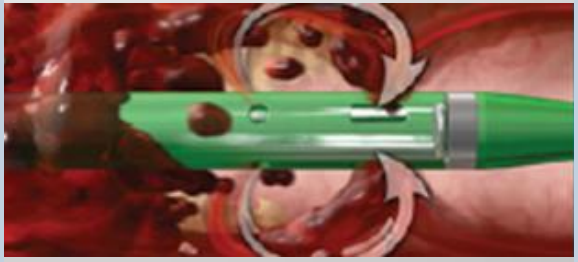
These techniques offer:

- A ***minimally invasive*** procedure
- Potential to minimize treatment time
- ***Shorter treatment time***
- Possibility to reduce the risk of PE
- Possibility to eliminate or decrease dose and duration thrombolytic
- Potential for ***quick resolution of signs and symptoms***
- Provide improved short term & hopefully long term outcomes

An option for DVT thrombus Removal

Thrombectomy System





MECHANISM OF ACTION

1. The AngioJet Console monitors and controls the system.
2. The Console energizes the pump which sends pressurized saline to the catheter tip.
3. Saline Jets travel backwards to create a low pressure zone causing a vacuum effect.
4. Thrombus is drawn into the in-flow windows and the jets push the thrombus back down the catheter.
5. Thrombus is evacuated from the body and into the collection bag.

Catheter Directed Lytics

Pharmacologic thrombolytic agent delivery through an infusion catheter and/or wire that is embedded within the thrombosed vein being treated.

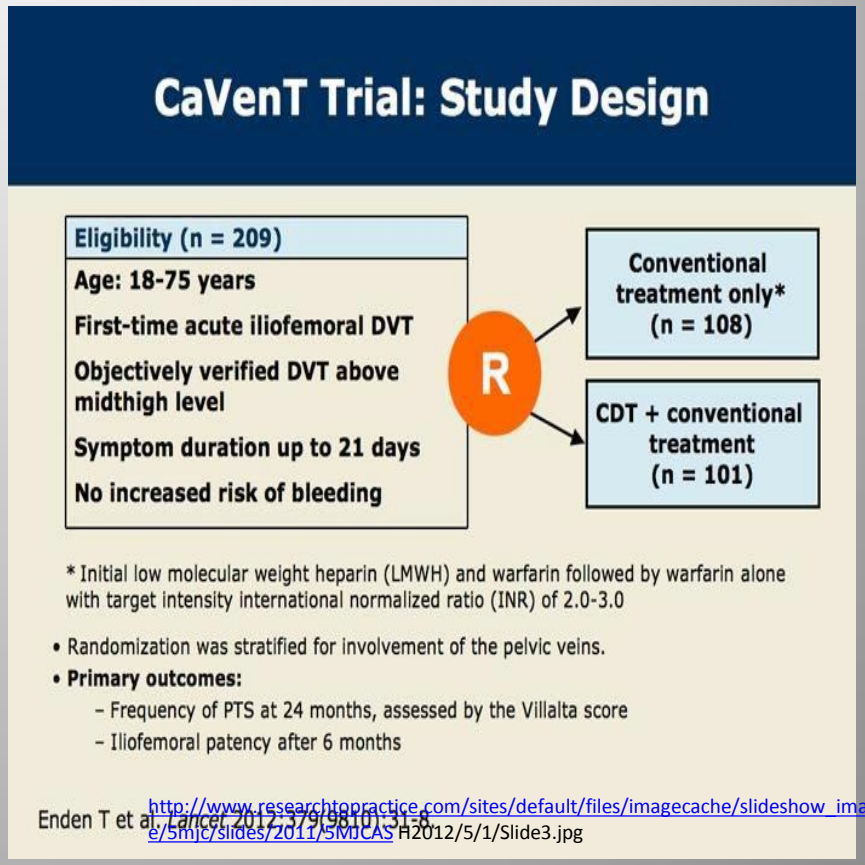
Thrombolytic therapy requires careful monitoring. In most clinical practices, this may occur in an intensive care unit or step-down unit.

Quality Improvement Guidelines for the Treatment of Lower Extremity Deep Vein Thrombosis with Use of Endovascular Thrombus Removal
J Vas Interv Radiol 2006; 17:435-448

Catheter-Directed Thrombolysis for Deep Vein Thrombosis (CaVenT) - Norway

- n=176 IFDVTpatients followed to 5 years
- 1:1 randomization to catheter-directed thrombolysis (CDT) and anticoagulation vs. anticoagulation alone
- End-point: assess development of PTS
- 43% CDT group vs. 71% of control developed PTS (p = 0.0001)
- QOL scores not statistically significant between groups
- 28% Absolute risk reduction

(95% CI 14-42%)



Enden T et al. *Lancet* 2012;379(9810):31-8.

http://www.researchtopractice.com/sites/default/files/imagecache/slideshow_image/5mjc/slides/2011/SMICAS H2012/5/1/Slide3.jpg

PEARL Registry (Boston Scientific)

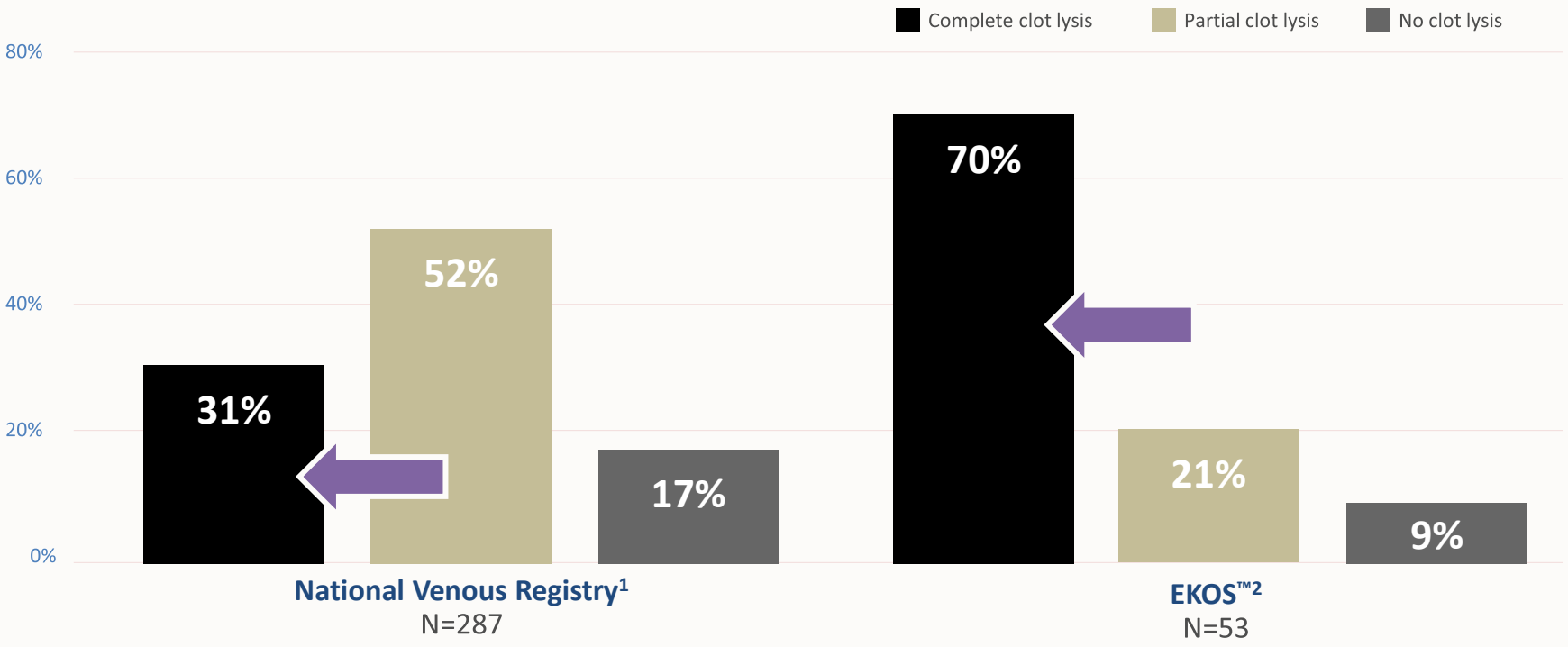
- n=329 patients with image-confirmed DVT (**66% iliac involvement**)
- Treatment groups
  - Rheolytic thrombectomy (RT) without lytics (4%)
  - ***Pharmacomechanical catheter-directed therapy (PCDT) (35%)***
  - PCDT and catheter-directed thrombolysis (CDT) (52%)
  - RT and CDT (9%)
- End-point: assess procedure/patient outcomes of endovascular treatment of DVT with RT

PEARL Registry

- Median procedure times
  - RT alone: 1.4 h
  - PCDT: 2 h
  - PCDT/CDT: 22 h
  - RT/CDT: 41 h (P = 0.05, Kruskal–Wallis test)
- 36% procedures done within 6 hours; 86% required ≤ 2 sessions
- 3-, 6-, and 12-month freedom from re-thrombosis rates
  - 94%, 87%, and 83%, respectively
- Physical/mental SF-12 QOL scores sig. improved 3-, 6- & 12-month f/u
- Interpretation: ***PCDT*** may reduce need/duration of CDT for DVT tx

Acoustic Pulse Thrombolysis™

Greater clot clearance than CDT

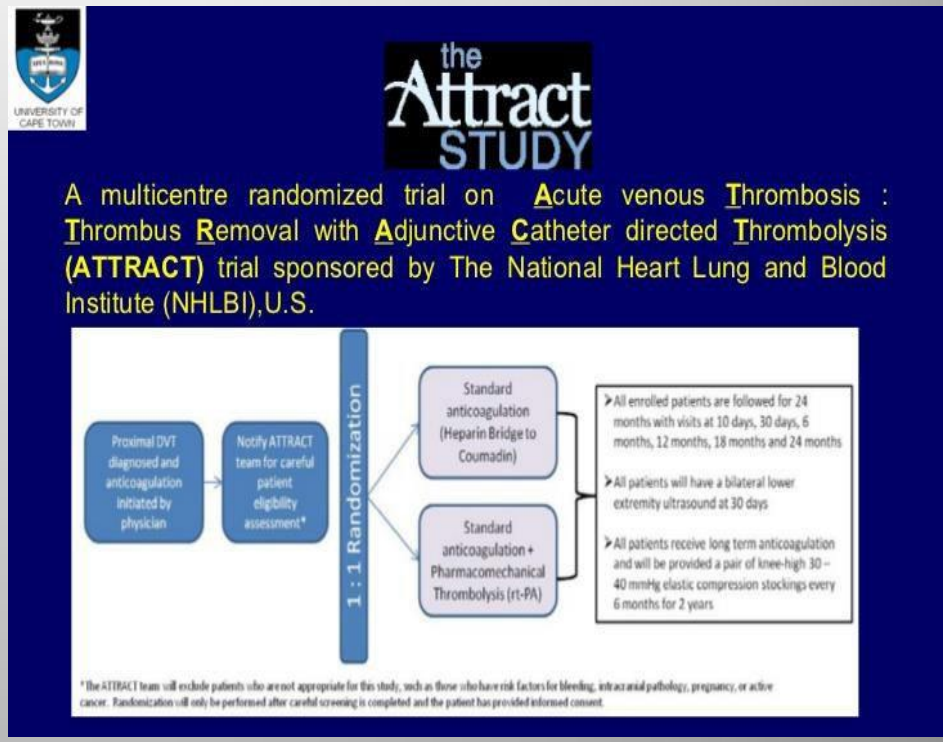


1. Mewissen MW et al. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. Radiology.1999; Apr;211(1):39-49
2. Parikh S et al. Ultrasound-accelerated thrombolysis for the treatment of deep vein thrombosis: initial clinical experience. J Vasc Interv Radiol. 2008; Apr;19(4):521-8

EKOS™ Acoustic Pulse Thrombolysis™ is a minimally invasive system for accelerating thrombus dissolution.

The "Open Vein Hypothesis"

- Development of PTS is associated with persistent venous thrombosis
- Does active elimination of DVT prevent PTS?
- Support comes from studies linking:
  - Poor thrombus clearance to venous ***valve dysfunction and recurrent VTE***
  - Residual venous thrombus or ***valve incompetence*** and PTS
  - Systemic thrombolysis, surgical thrombectomy or CDT to reduced incidence of PTS



ATTRACT Trial Design

- Multicenter, randomized, open-label, assessor-blinded, parallel two- arm, controlled clinical trial sponsored by National Heart, Lung, and Blood Institute of the U.S. National Institutes of Health

- SIR Foundation, Boston Scientific, BSN Medical, Covidien/Medtronic,
- and Genentech provided additional support

- 692 subjects enrolled in 56 US Centers followed for 24 mo
  - 337 randomized to PCDT
  - 355 randomized to no PCDT

ATTRACT Trial Objectives

- Primary objective:
  - Determine if PCDT with standard DVT therapy reduces development of PTS after 24 month follow-up compared to standard DVT therapy alone

- Secondary objectives:
  - Evaluate for major bleeding, symptomatic VTE and death
  - Venous disease-specific QOL
  - Relief of acute DVT symptoms
  - Pretreatment predictors of response to PCDT in preventing PTS
  - Compare medical costs and cost-effectiveness
  - Determining technical, anatomical and physiologic endpoints of therapy

ATTRACT Trial – Standard DVT Therapy

- Weight-based low molecular weight heparin or IV unfractionated heparin then Warfarin
- International guidelines for INR 2-3, duration of therapy (3 months or longer)
- 30-40 mmHg knee-high elastic compression stockings at 10 day follow-up

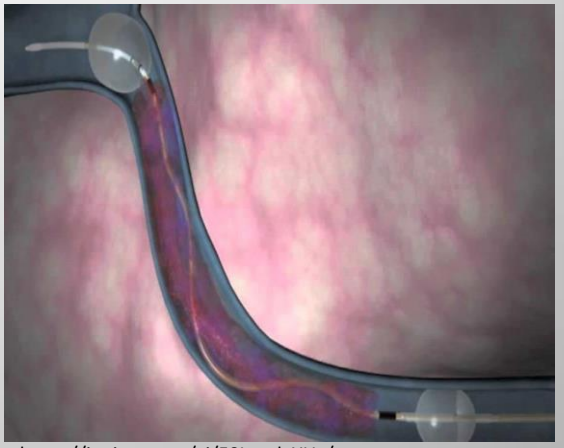
https://cdn.shopify.com/s/files/1/0750/5967/products/0845-BG_1024x1024.jpg?v=1431722878

ATTRACT Trial – PCDT Intervention

- One of three methods for rt-PA delivery (max 25 mg initially; max 35 mg total)

    1. "Isolated Thrombolysis" with Trellis Peripheral Infusion System (Covidien, Inc.)

    2. "PowerPulse Thrombolysis" with AngioJet Rheolytic Thrombectomy System (Boston Scientific)



https://i.ytimg.com/vi/50LzxuleYUc/maxresdefault.jpg

ATTRACT Trial – PCDT Intervention

- One of three methods for rt-PA delivery (max 25 mg initially; max 35 mg total)

http://www.angiodynamics.com/images/userfiles/Unifuseillustration.jpg

3. "Infusion-First Thrombolysis" with multisidehole catheter through thrombus, up to 1 mg/h rt-PA for max 30 hours

    - Subsequent therapy with balloon maceration, aspiration thrombectomy and/or mechanical thrombectomy allowed for residual thrombus

ATTRACT Trial – Endpoints and Efficacy

- ≥90% thrombus clearance with restored flow
- 35 mg maximum rt-PA dose or 30 h maximum infusion time reached
- Overt clinical bleeding or other complications necessitating cessation
- Evaluation for PTS in index limb at 6-24 months after randomization
- Villalta PTS scoring used
  - Combines patient and clinician evaluation
  - PTS defined as Villalta score > 5 or presence of ulcer

ATTRACT Trial
"The Bad & Ugly"

- ***PCDT not found to reduce incidence of PTS*** compared to AC alone
  - PTS 46.7% for PCDT vs 48.2% for no-PCDT (p= 0.56)
  - Recurrent VTE higher in PCDT vs no-PCDT (12.5% vs 8.5%; p=0.09)
  - Major and any bleeding rates statistically higher in PCDT arm (1.7% vs 0.3%; p=0.49 and 4.5% vs 1.7%; p=0.034) – in line with prior studies
    - NO intracranial or fatal hemorrhages

ATTRACT Trial

- IFDVT vs femoropopliteal DVT (FPDVT)
  - Trends to more ***benefit in IFDVT***
  - Study not powered to sufficient power to statistically significant differences between subgroups

ATTRACT Trial
"The Good"

- Leg pain and swelling significantly improved in PCDT vs. no-PCDT out to 30 days (p=0.019 and p=0.05)
  - ***PCDT helpful for acute symptoms***

- 25% fewer patients in PCDT arm developed ***moderate or severe PTS*** vs no-PCDT (17.9 % vs 23.7%; p=0.035)
  - "Open Vein hypothesis"

ATTRACT Trial – Results SIR 2017 – "The Good"

- In IFDVT mod-severe PTS was 18.4% vs 28.2% in PCDT vs no-PCDT

- In FPDVT little difference (17.1% vs 18.1% moderate to severe PTS)

- PCDT was less effective in patients ≥ 65 y/o

ATTRACT Trial
Summary and Learning points

- Ambitious well-designed RCT, failed primary endpoint, but **not the end**
- Helps us strategize for appropriate care
- **Who to and not to treat**
  - Same as CaVenT: *iliofemoral DVT, younger and functional patients*
  - Femoropopliteal DVT alone patients do not derive same benefit
  - Older patients do not derive same benefit
  - Prevent bleeding and cost in inappropriate patients

ATTRACT Trial Learning points

- Do we fully understand the pathophysiology of PTS?
  - ***Is the "Open Vein Hypothesis" enough?***

- We know thrombolysis works, but are ***recent tech advances*** enough to merit further trials (Boston-Scientific ZelanteDVT, Inari Flow-Triever, Penumbra Indigo, Argon Cleaner, etc.)?

ATTRACT Trial Learning points

- Same-session therapy vs. prolonged ICU time for thrombolysis?
  - Cost and resource analysis
  - Patient experience

- Role of IVUS in treatment of iliofemoral disease?
  - Likely to be an integral component of development of new technologies

- Femoropopliteal subgroup did not derive benefit
  - Did we look sufficiently at the ***iliac segments for evidence of compression?***

A Word on Iliac Vein Compression

- **80% of Iliofemoral DVT have underlying external iliac venous compression**

- Chang, et al.JVIR;15:249-56

MAY-THURNER

IVC FILTER OCCLUSION

ANEURYSMS, ARTERIAL GRAFTS

TUMORS,CYSTS

SURGICAL INJURY

RADIATION FIBROSIS

Iliac Venous Compression
Diagnosis

- CT/MR Venogram
  - Anatomic details
  - ***Do NOT evaluate flow***
  - ***Timing of contrast*** injection-flow issues
  - Dependent upon facility and radiology interest

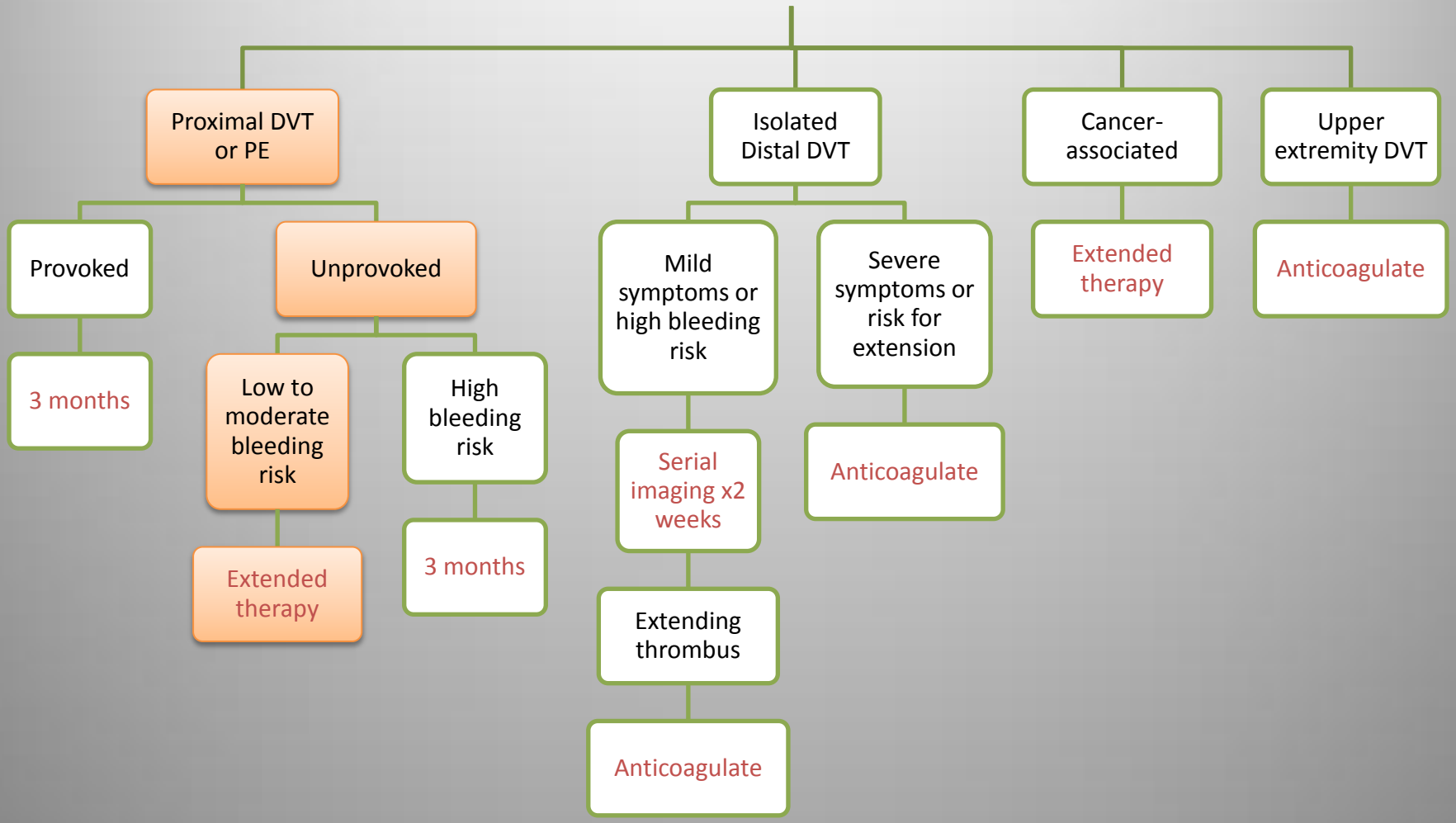
Definitive diagnosis

- Venogram
  - Anatomic diagnosis
  - Assessment of flow: femoral inflow/iliac outflow
  - Collaterals
  - ***Will miss some stenosis and webs***

Intra Vascular Ultrasound
IVUS

- The anatomic gold standard
- Evaluate compression in CFV, Iliac veins: morphology and CSA
- Evaluation of CFV, bilateral iliac veins and IVC
- Choosing diameter and length of balloon/stent
- Post stenting assessment

Word on Duration of Therapy



Conclusion

50%+ of DVT patients treated with the standard of care risk developing **Post Thrombotic Syndrome**[1]

There may be a potential benefits of adding Interventional thrombolysis, mechanical thrombectomy, and/or pharmacomechanical thrombectomy for the treatment of DVT in ***selected patients.***

[1]Centers for Disease Control and Prevention. Venous Thromboembolism (Blood Clots). Data & Statistics. http://www.cdc.gov/ncbddd/dvt/data.html. Accessed October 5, 2015.

Moving Forward

Multidisciplinary team approach to in-hospital DVT

Create best practice model

Develop treatment pathways to benefit patients for quicker recovery

Reduce the potential risks for those that develop DVT

Decrease hospital stay and cost associated with DVT

Potential to improve short and long term outcomes

Thank you

Questions