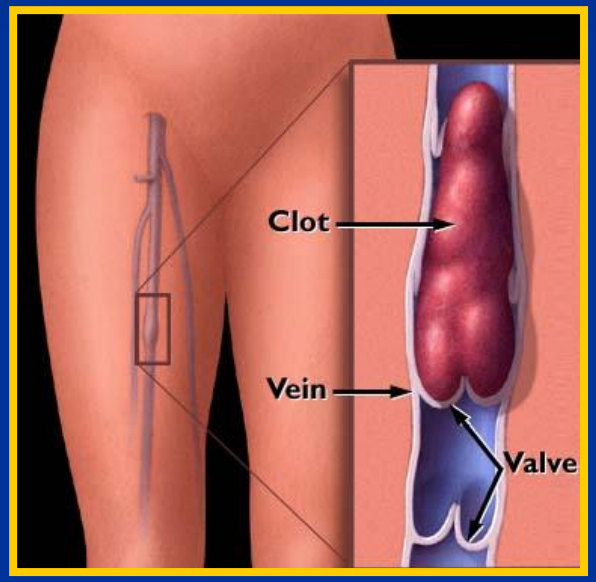
Modern Management of Deep Vein Thrombosis



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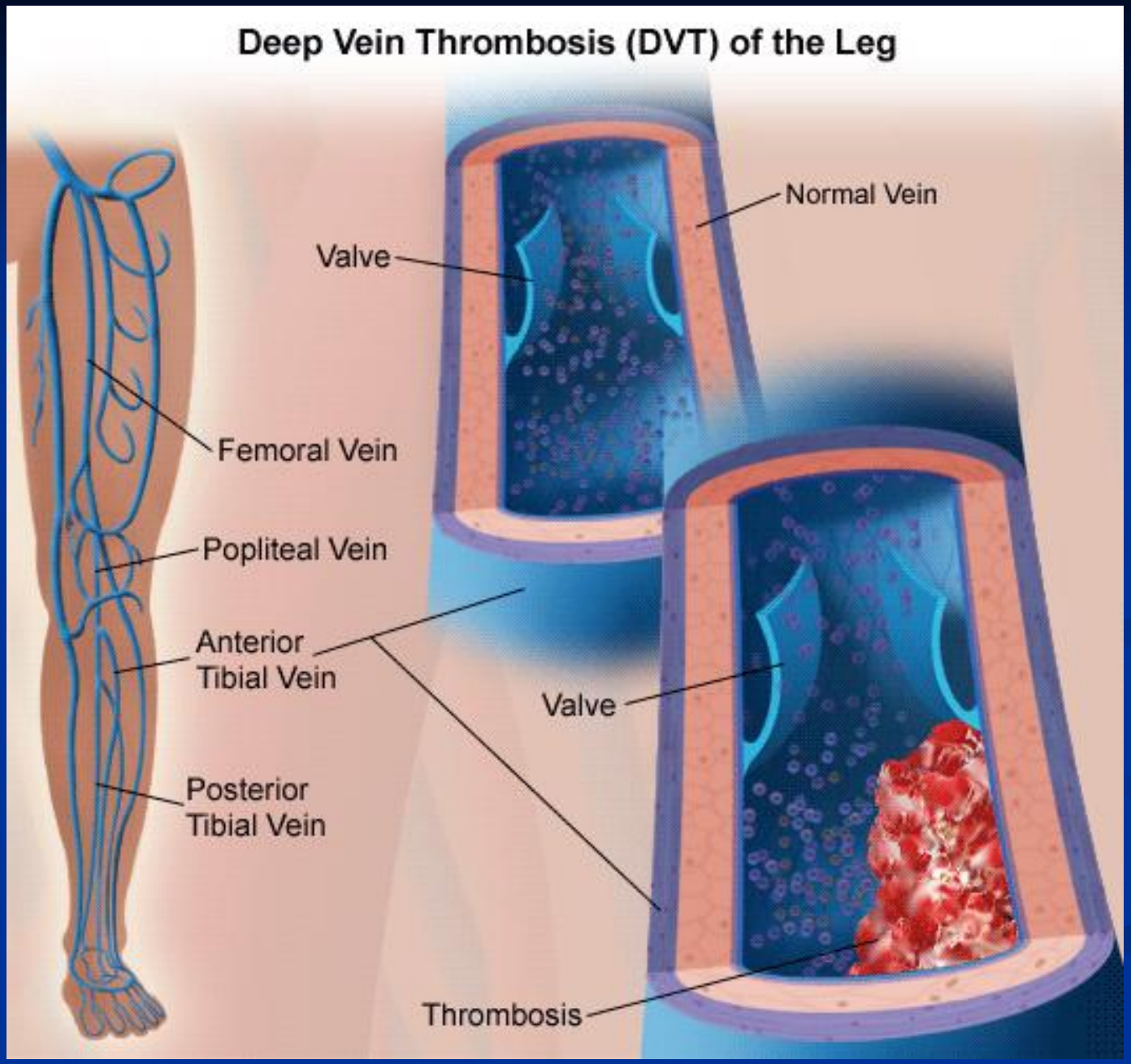

Deep Vein Thrombosis (DVT) of the Leg
Normal Vein
Valve
Femoral Vein
Popliteal Vein
Anterior
Tibial Vein
Valve
Posterior
Tibial Vein
Thrombosis

Venous Thromboembolism (VTE)

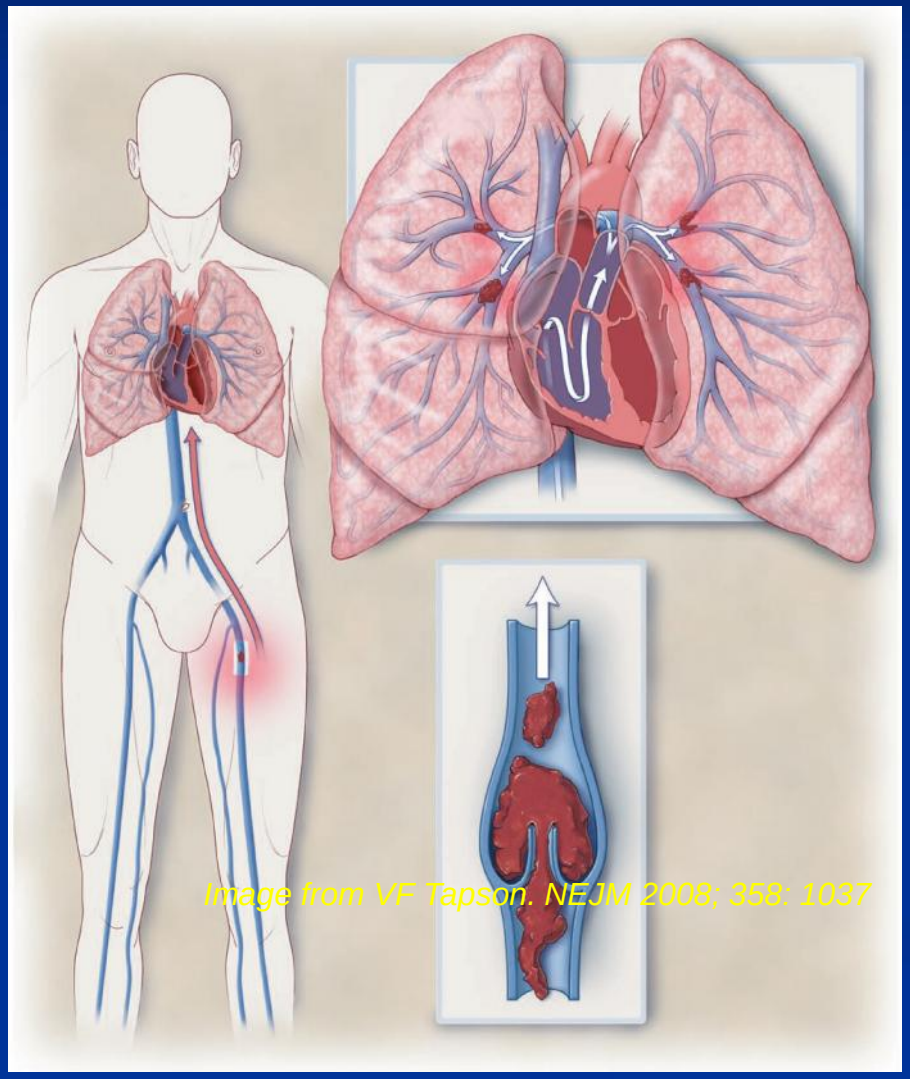


Image from VF Tapson. NEJM 2008; 358: 1037

Pulmonary embolism (PE)

40% of non-fatal cases

Severity depends on size and cardiopulmonary reserve

Sub-segmental PE has important risk of recurrence

30% to 70% have residual DVT

Deep-vein thrombosis (DVT)

60% of non-fatal cases

Proximal DVT prognostic marker for recurrence and mortality

Epidemiology of Venous Thrombo-Embolism (DVT+PE) Global & India

3rd most common cause of CV disease[1]

Is it underestimated in India?

1. Goldhaber SZ. Pulmonary embolism thrombolysis: a clarion call for international collaboration. *J Am Coll Cardiol* 1992;19:246-7.
2. Cohen AT et al. Thromb Haemost. 2007;98:756-64;
3. Roger VL et al. Circulation 2012;125:e2-220;
4. Ray G et al. VTE- Indian Perspective, Med Update 2010; 20: 329-34.

DVT/PE - Extent of the Problem

- 70-113 cases per 100,000 population per year
- No gender difference, however recurrent DVT is seen in Males > Females
- More common in winter than in summer by 10-15%
- DVT/PE is the third leading cardiovascular killer after heart attack and stroke
- DVT/PE causes more people to die annually than breast cancer and AIDs combined

Points of Discussion

- 1. Causes of Deep Vein Thrombosis
- 2. Clinical Presentation
- 3. Diagnostic Algorithms
- 4. Treatment of Acute DVT
- 5. Treatment of Chronic DVT
- 6. Long term Anti coagulation

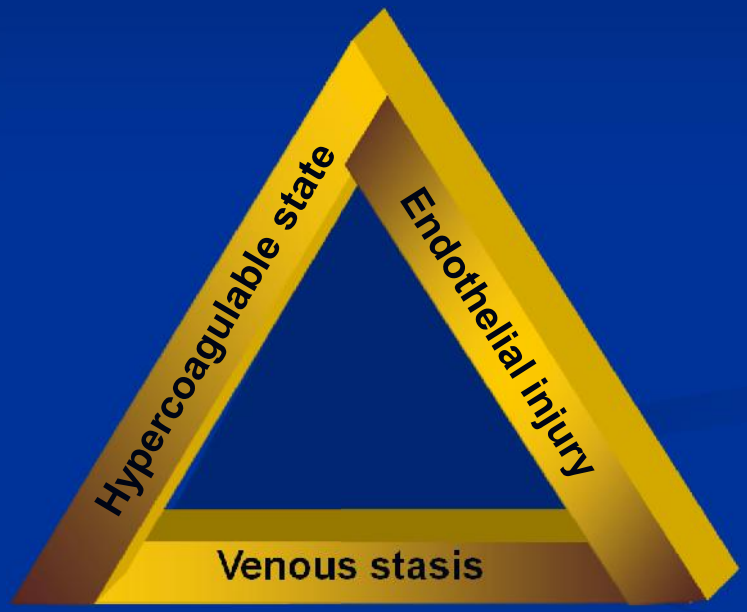
Why does DVT Occur ? Pathophysiology

- VIRCHOW'S TRIAD — A major theory which proposes that VTE occurs as a result of:

- Alterations in blood flow (i.e., stasis)
- Vascular endothelial injury
- Alterations in the constituents of the blood (i.e., inherited or acquired hypercoagulable state)

Virchow's triad

- Acute phase postop
- Cancer
- Thrombophilia
- Estrogen therapy
- Pregnancy and postpartum period
- Inflammatory bowel disease



- Surgery
- Trauma
- Indwelling catheter
- Atherosclerosis
- Heart valve disease or replacement

- Immobility or paralysis
- Heart failure
- Venous insufficiency or varicose veins
- Venous obstruction from tumour, obesity or pregnancy

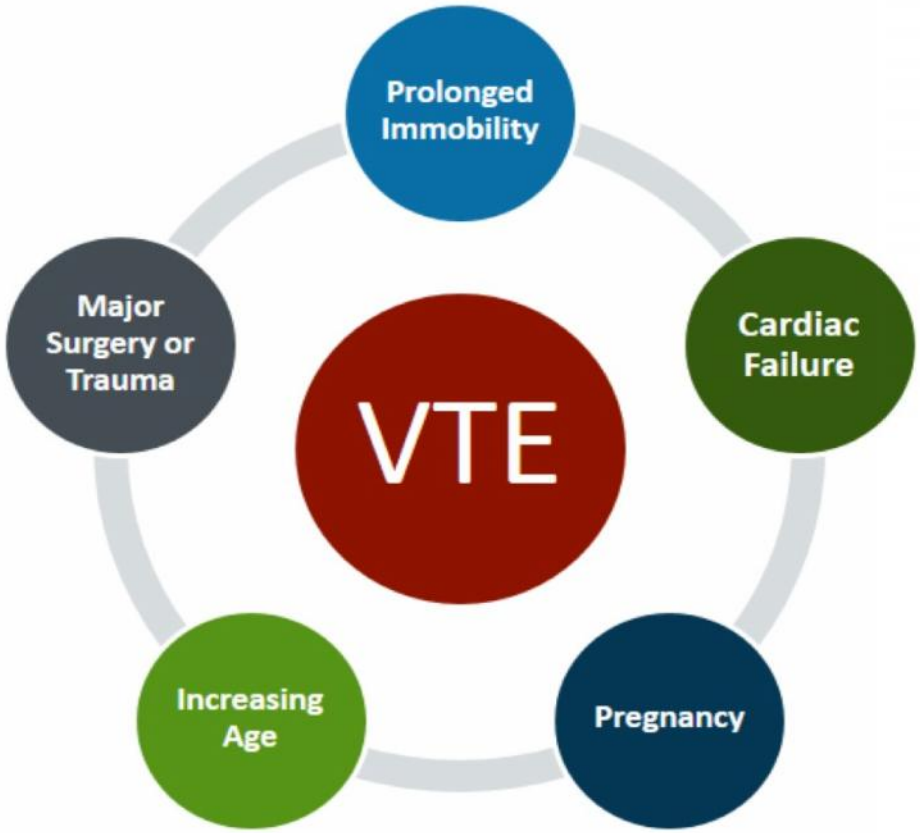
Virchow R, ed. *Gesammelte Abhandlungun zur Wissenschaftichen Medicin*. Von Meidinger Sohn, Frankfurt, 1856

Clinical Presentations of Venous Thrombo Embolism (VTE)

- **Provoked (70% of all patients)**
  - Associated with known risk factors
  - Hospital, surgery, cancer, medical illness
  - Risk factors may be continuing (cancer, APLA)
  - If risk factor reversible (transient), 2% per year recurrence after 3 months of anticoagulant therapy
- **Unprovoked - Idiopathic (30% of all patients)**
  - Absence of identifiable risk factor
  - Also called "idiopathic"
  - 7% to 11% per year recurrence for DVT or PE if anticoagulant therapy stopped after 3, 6,12 or 24 months

Kearon C, Akl E. Blood 2014; 123 (12) 1794-1801.
Boutitie F et al. BMJ 2011, May 24;342:d3036

Most Common Causes of VTE



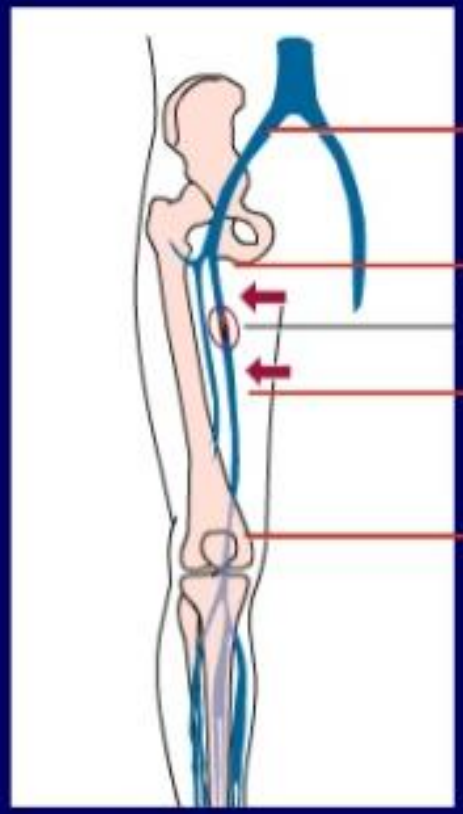
Anderson FA, et al. *Circulation*. 2003;107:I9-I13.

- Prevalence of DVT in hospitalized patient groups

Spinal cord injury	60-80%
Major trauma	40-80%
Hip/Knee arthoplasty or hip fracture surgery	40-60%
Critical care	10-80%
Stroke	20-50%
General surgery	15-40%
Major gynaecological surgery	15-40%
Neurosurgery	15-40%
Major urologic surgery	15-40%
Medical patients	10-20%

Classification

- Acute (< 2 weeks)
- Recurrent DVT
- Anatomical



Ilio-femoral → Bilateral / (L) ilio-femoral / Multi segmental

Profunda femoris vein

Femoro-popliteal

Knee

Proximal

Distal

Clinical Presentation

Acute DVT may present as

- Asymptomatic
- Symptomatic
- Complicated → Phlegmasia → Caerulea dolens (PCD)
  - Phlegmasia → Alba dolens (PAD)
  - Complicated → PTE

Symptoms:

Pain- exacerbated by ambulation, relieved by rest

Swelling- below knee (distal DVT), Up to groin (proximal DVT)

Erythema

Signs and symptoms of DVT and PE due to 3 reasons:

- 1. Venous obstruction
- 2. Associated inflammatory response of vessel wall
- 3. Fragmentation of clot with embolisation to pulmonary arteries.

Diagnosis of DVT
- an algorithmic approach

Pretest Probability

D Dimer

Venous US

Clinical Probability of DVT

Common risk factors

- Presence of an acute infectious disease
- Age older than 75 years
- Cancer
- History of prior VTE
- Obesity
- Surgery
- Immobility.
- Genetic thrombophilia is identified in 30% of patients with idiopathic venous thrombosis

Symptoms

- Edema - Most specific symptom
- Leg pain - Occurs in 50% of patients but is nonspecific
- Tenderness - Occurs in 75% of patients
- Warmth or erythema of the skin over the area of thrombosis
- Clinical symptoms of pulmonary embolism (PE) as the primary manifestation

Clinical Probability

- The Wells clinical prediction guide quantifies the pretest probability of DVT.
- The model reliably stratifies patients into high-, moderate-, or low-risk categories.
- Wells score + results of objective testing simplifies the clinical workup of patients with suspected DVT.
- The Wells clinical prediction guide incorporates risk factors, clinical signs, and the presence or absence of alternative diagnoses.

Modified Wells Criteria

Clinical Parameter Score	Score
Active cancer (treatment ongoing, or within 6 mo or palliative)	+1
Paralysis or recent plaster immobilization of the lower extremities	+1
Recently bedridden for >3 d or major surgery <4 wk	+1
Localized tenderness along the distribution of the deep venous system	+1
Entire leg swelling	+1
Calf swelling >3 cm compared with the asymptomatic leg	+1
Pitting edema (greater in the symptomatic leg)	+1
Previous DVT documented	+1
Collateral superficial veins (nonvaricose)	+1
Alternative diagnosis (as likely or greater than that of DVT)	-2
Total of Above Score	
High probability	≥3
Moderate probability	1 or 2
Low probability	≤0

Diagnosis of DVT
- an algorithmic approach

Pretest Probability

D Dimer

Venous US

DVT D-dimer Level

- D-dimer fibrin fragments are present in fresh fibrin clot and in fibrin degradation products of cross-linked fibrin.
- Monoclonal antibodies specific for the D-dimer fragment are used to differentiate fibrin-specific clot from non–cross-linked fibrin and from fibrinogen.
- These specific attributes of the D-dimer antibodies account for their **high sensitivity for venous thromboembolism.**

DVT D-dimer

- D-dimer level may be elevated in any medical condition where clots form.
- D-dimer level is elevated in trauma, recent surgery, hemorrhage, cancer, and sepsis.
- Many of these conditions are associated with higher risk for DVT.
- **The D-dimer assays have low specificity for DVT; therefore, they should only be used to rule out DVT, not to confirm the diagnosis of DVT.**

DVT D-dimer

D-dimer results should be used as follows:

- A negative D-dimer assay result rules out DVT in patients with low-to-moderate risk and a Wells DVT score less than 2.
- All patients with a positive D-dimer assay result and all patients with a moderate-to-high risk of DVT (Wells DVT score ≥2) require a diagnostic study (duplex ultrasonography).

Diagnosis of DVT
- an algorithmic approach

Pretest Probability

D Dimer

Venous US

Imaging- Usually Venous Ultrasound

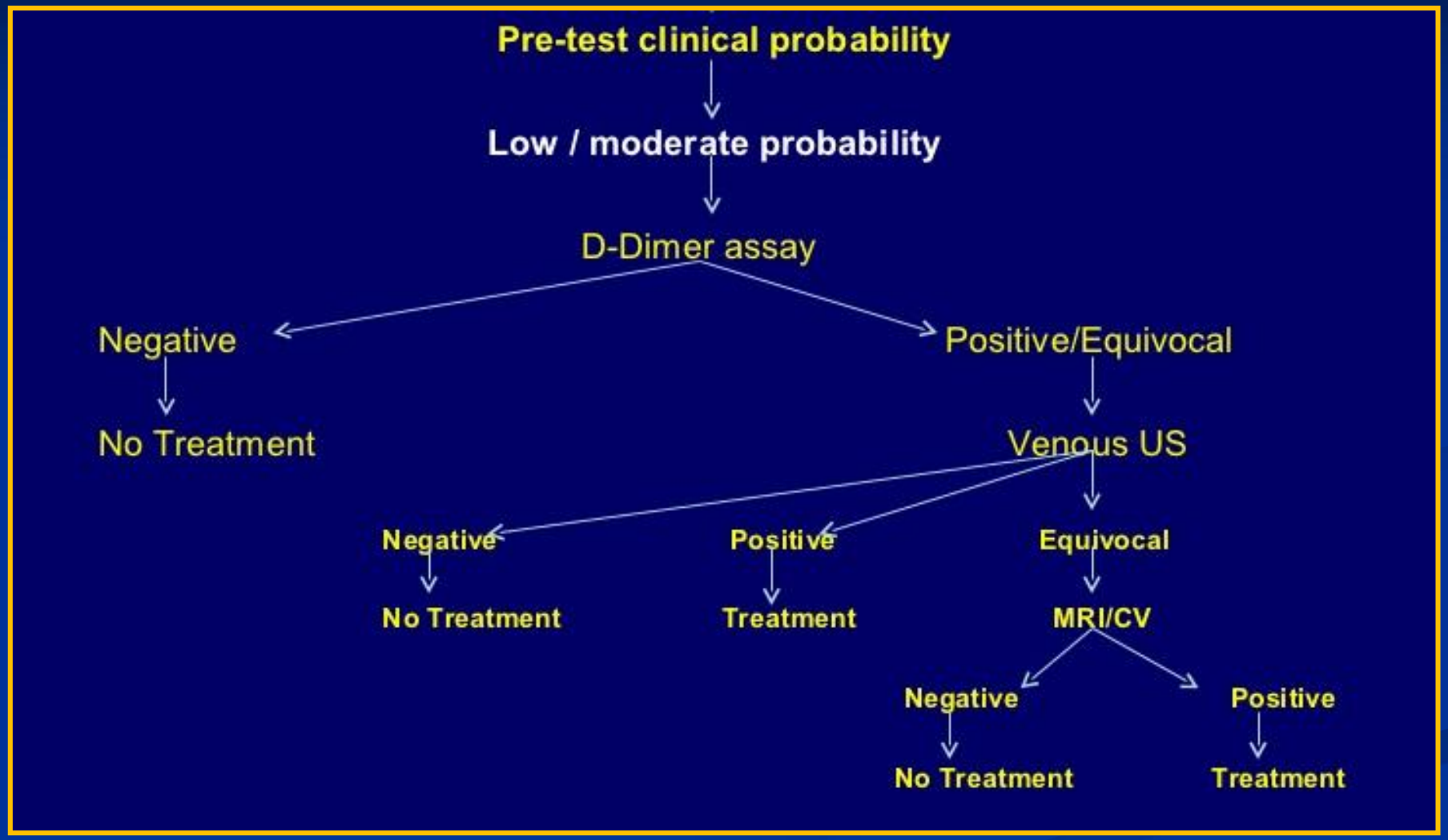
Imaging Modality	Advantages	Disadvantages
Compression Ultrasound	Sensitivity 97-100% and specificity of 98-99% for proximal DVT Non invasive, repeatable and widely available Higher sensitivity in detecting distal thrombosis	Difficult to perform in patients with morbid obesity, severe oedema, casts or other immobilization devices Decrease ability to visualize the Popliteal fossa in cases of distal DVT Operator dependent
CT Venography	Non invasive Can diagnose Pelvic DVT Concurrently exclude PE	Limited data
MRV	Highly accurate Safe during Pregnancy Non-invasive	Expensive Not readily available
Contrast Venography	"Gold Standard" Sensitivity approaches 100% Easily interpretable	Invasive Requires specialized equipment Rare but serious side effects

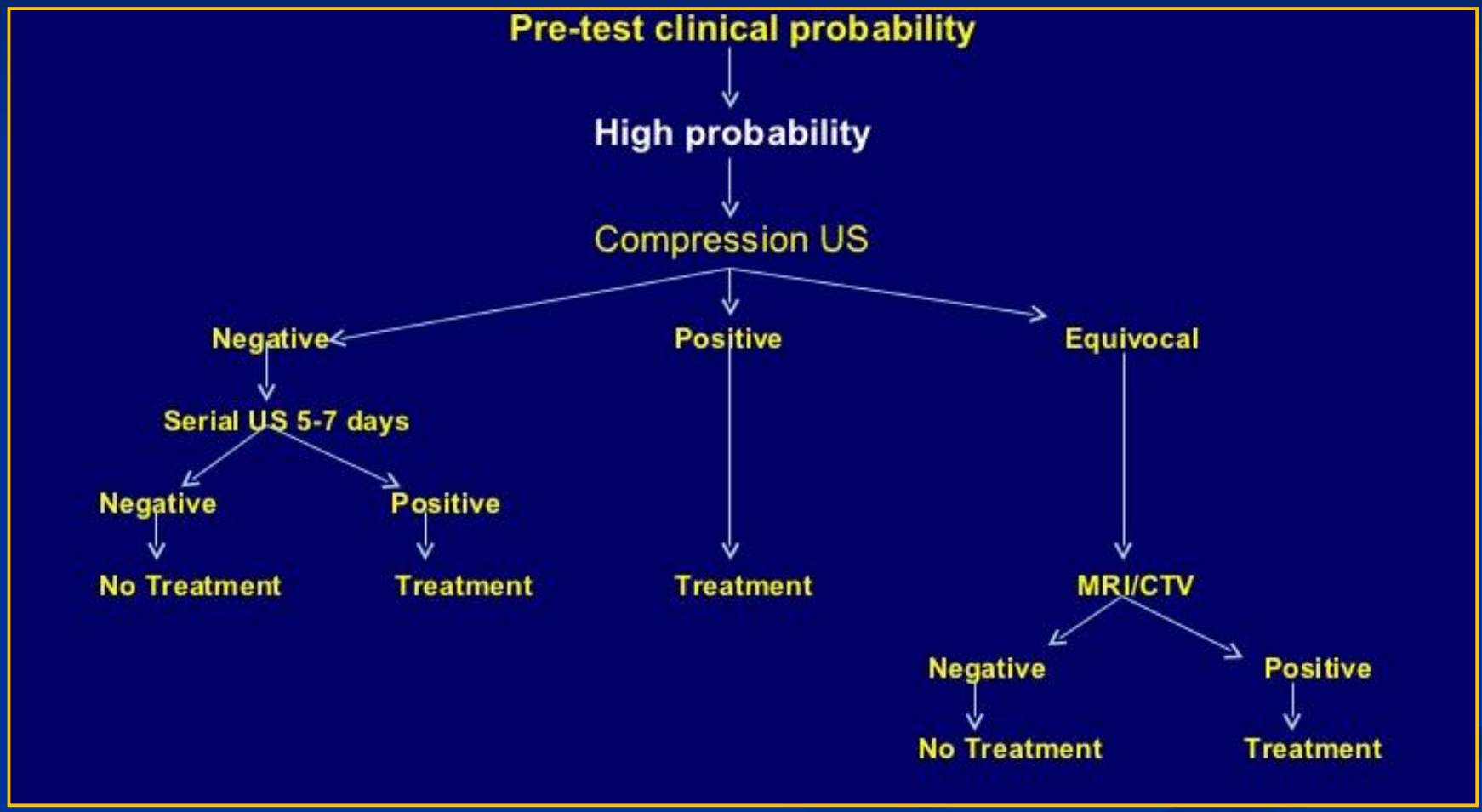
Diagnosis of DVT
- an algorithmic approach

Pretest Probability

D Dimer

Venous US


Pre-test clinical probability
Low / moderate probability
D-Dimer assay
Negative
No Treatment
Positive/Equivocal
Venous US
Negative
No Treatment
Positive
Treatment
Equivocal
MRI/CV
Negative
No Treatment
Positive
Treatment


Pre-test clinical probability
High probability
Compression US
Negative
Positive
Equivocal
Serial US 5-7 days
Negative
Positive
No Treatment
Treatment
Treatment
MRI/CTV
Negative
Positive
No Treatment
Treatment

Should we Screen For A Hyper - coagulable State in every case of DVT ?

- A biologic risk factor for venous thrombosis can be identified in over 60 percent of Caucasian patients with idiopathic DVT.
- However, more than 50 percent of thrombotic events in patients with inherited thrombophilia are associated with an accompanying acquired risk factor (e.g., surgery, pregnancy, use of oral contraceptives).

Screening For A Hyper-coagulable State

- There is currently no consensus regarding whom to test for inherited thrombophilia.
- Initial thrombosis occurring prior to age 50 without an immediately identified risk factor (i.e., idiopathic or unprovoked venous thrombosis)
- A family history of venous thromboembolism
- Recurrent venous thrombosis
- Thrombosis occurring in unusual vascular beds such as portal, hepatic, mesenteric, or cerebral veins
- A history of warfarin-induced skin necrosis, which suggests protein C deficiency

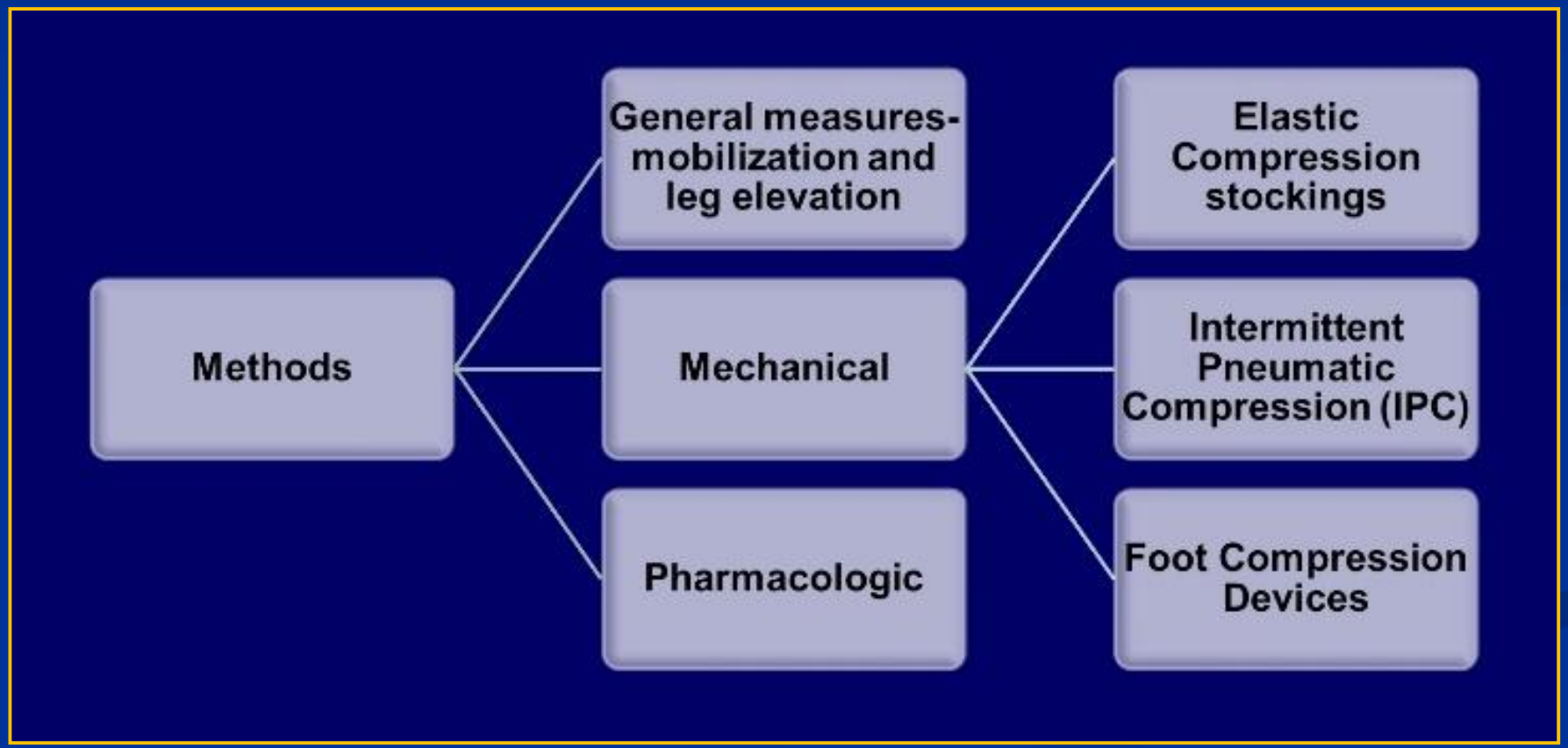
Prevention of DVT

Degree of Thromboembolism Risk in Surgical Patients without Prophylaxis

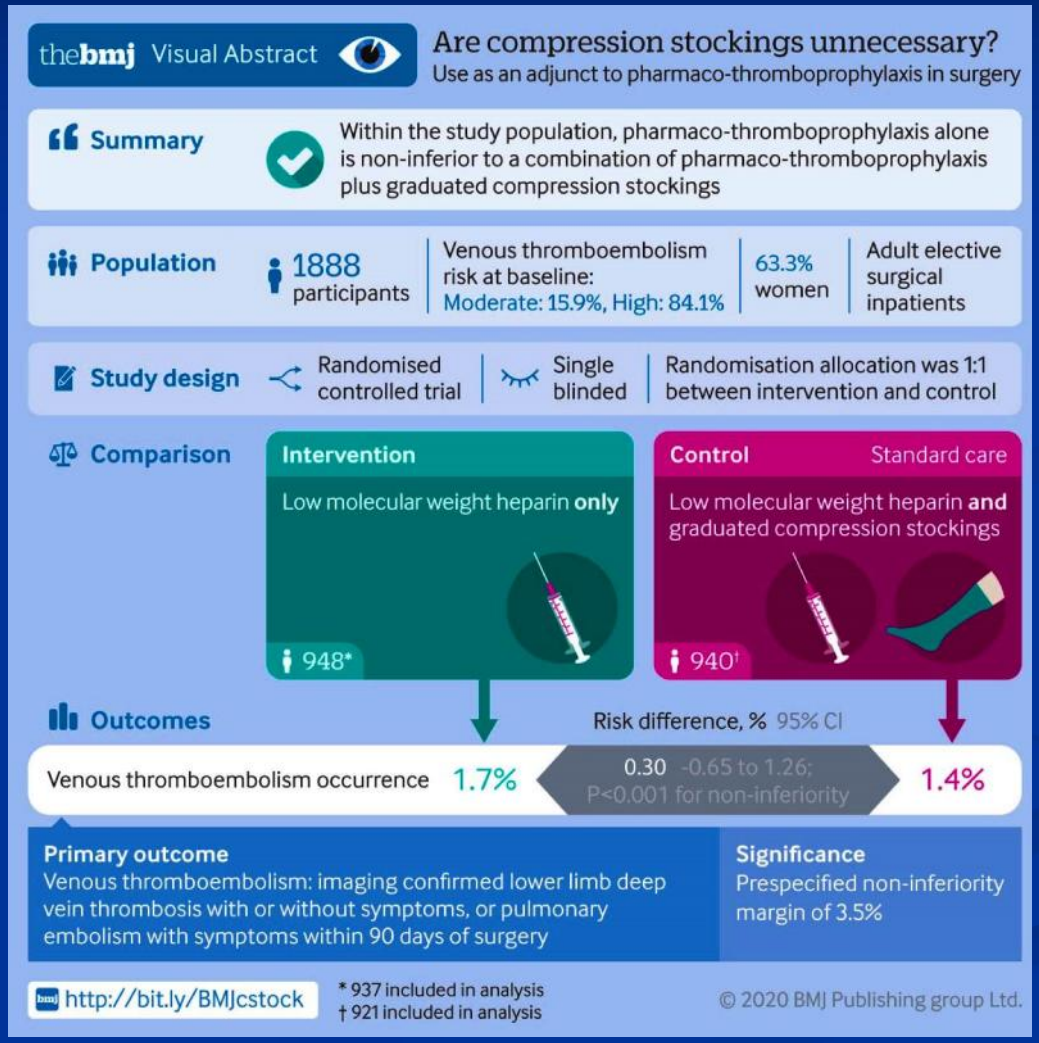
Risk level	Calf DVT (%)	Proximal DVT (%)	Clinical PE (%)	Fatal PE (%)
Low risk Minor surgery in patients aged <40 yr with no additional risk factors	2	0.4	0.2	<0.01
Moderate risk Minor surgery in patients with additional risk factors Surgery in patients aged 40–60 y with no additional risk factors	10-20	2-4	1-2	0.1-0.4
High risk Surgery in patients >60 y or with additional risk factors (e.g., prior VTE, cancer)	20-40	4-8	2-4	0.4-1.0
Highest risk Surgery in patients with multiple risk factors (age >40 y, cancer, prior VTE) Hip or knee arthroplasty, hip fracture surgery	40-80	10-20	4-10	0.2-5

dapted from: Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA, Wheeler HB. Prevention of venous thromboembolism. CHEST Journal. 2001 Jan 1;119(1_suppl):132S-75S.

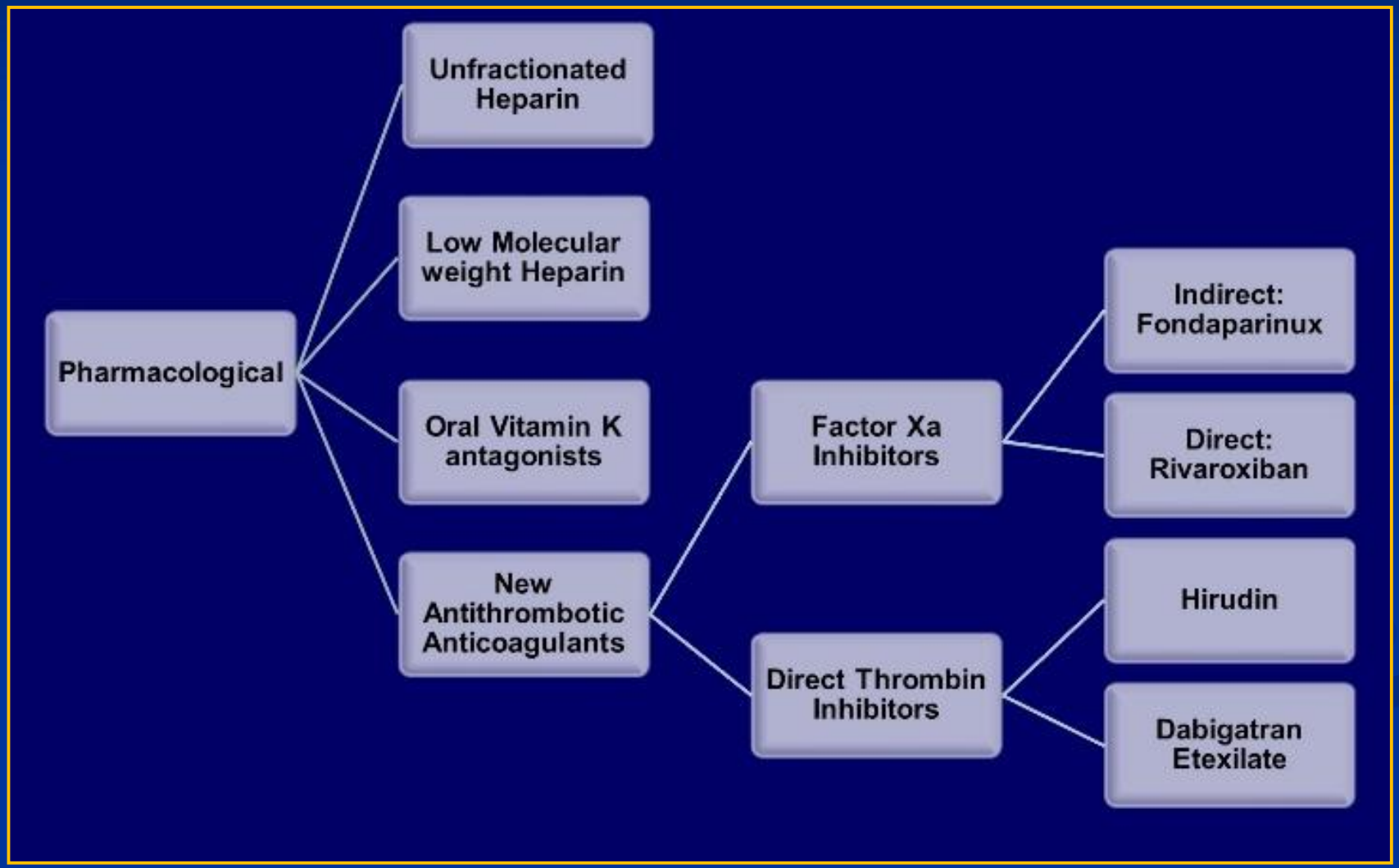
Prevention of DVT in High Risk Patients



Compression stockings not necessary in surgical patients !



Prevention of DVT in High Risk Patients

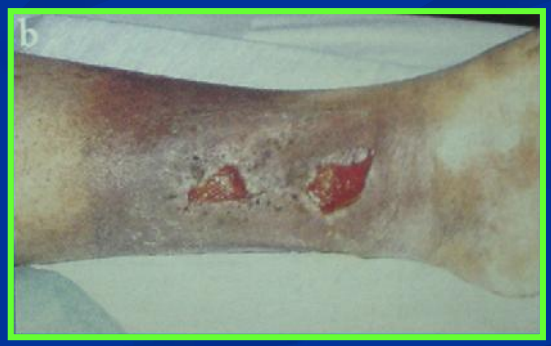


Importance of Preventing, Diagnosing and Treating VTE

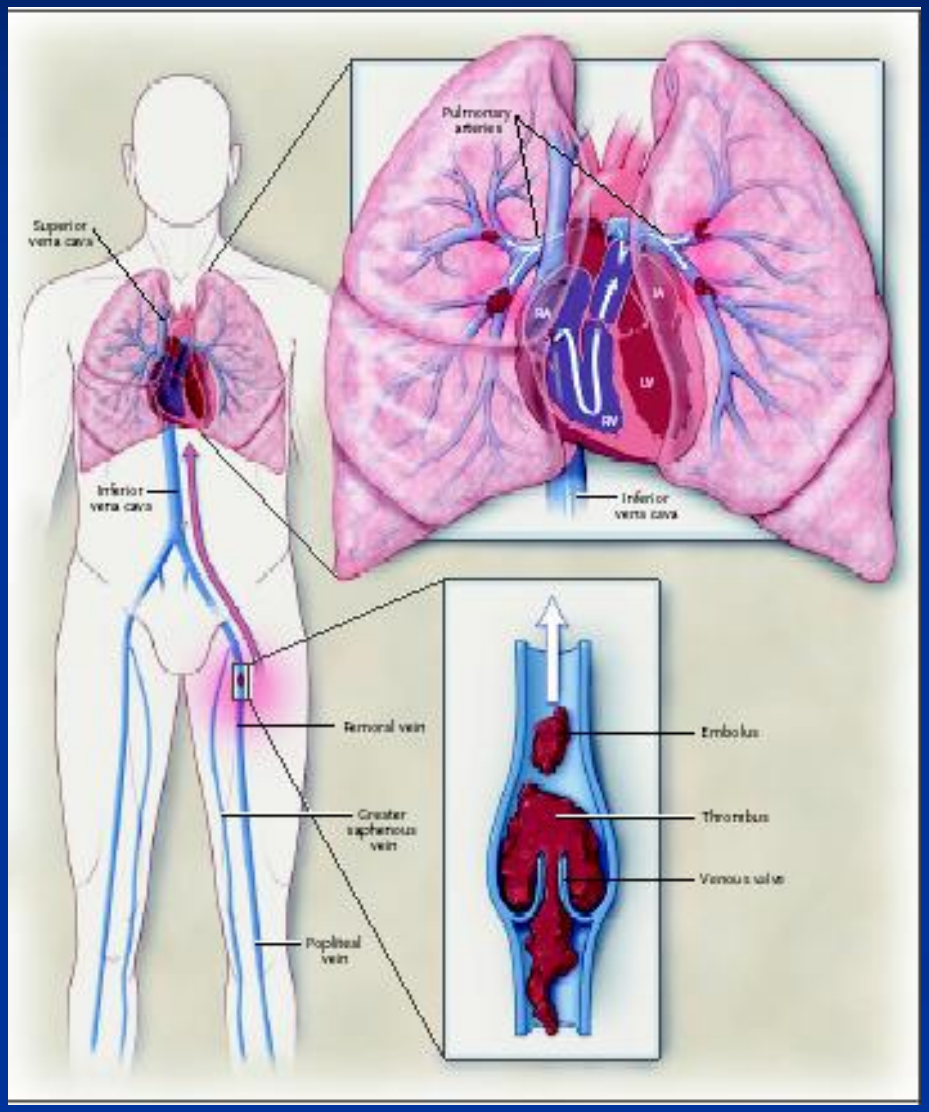
- Prevent death from pulmonary embolism
- Prevent symptomatic recurrent VTE 25% risk of symptomatic recurrent VTE during 3 months if inadequate therapy
- Prevent and/or reduce morbidity from
  Post-thrombotic syndrome (PTS) : 25% at 2 years
  Chronic pulmonary hypertension : 4% at 2 years
- Minimize the risk of bleeding and other side effects of treatment

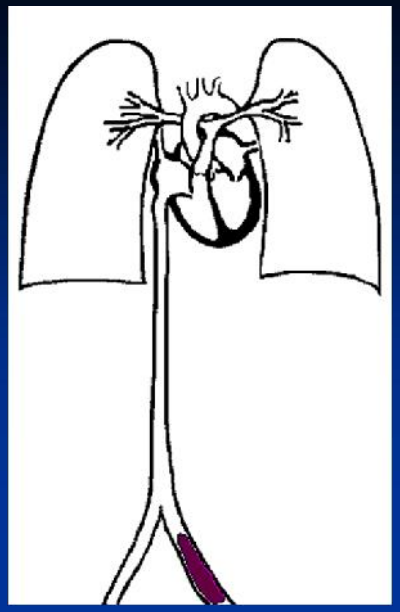
Why is it important to treat VTE ?

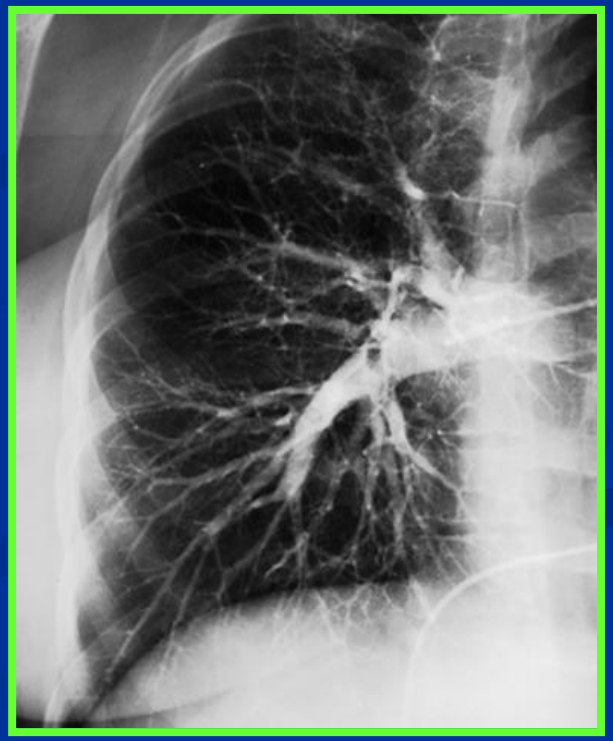
- Acute Complications:
  - Pulmonary Embolism
  - Phlegmasia
  - Venous Gangrene
- Late Complication
  - Post Thrombotic Syndrome

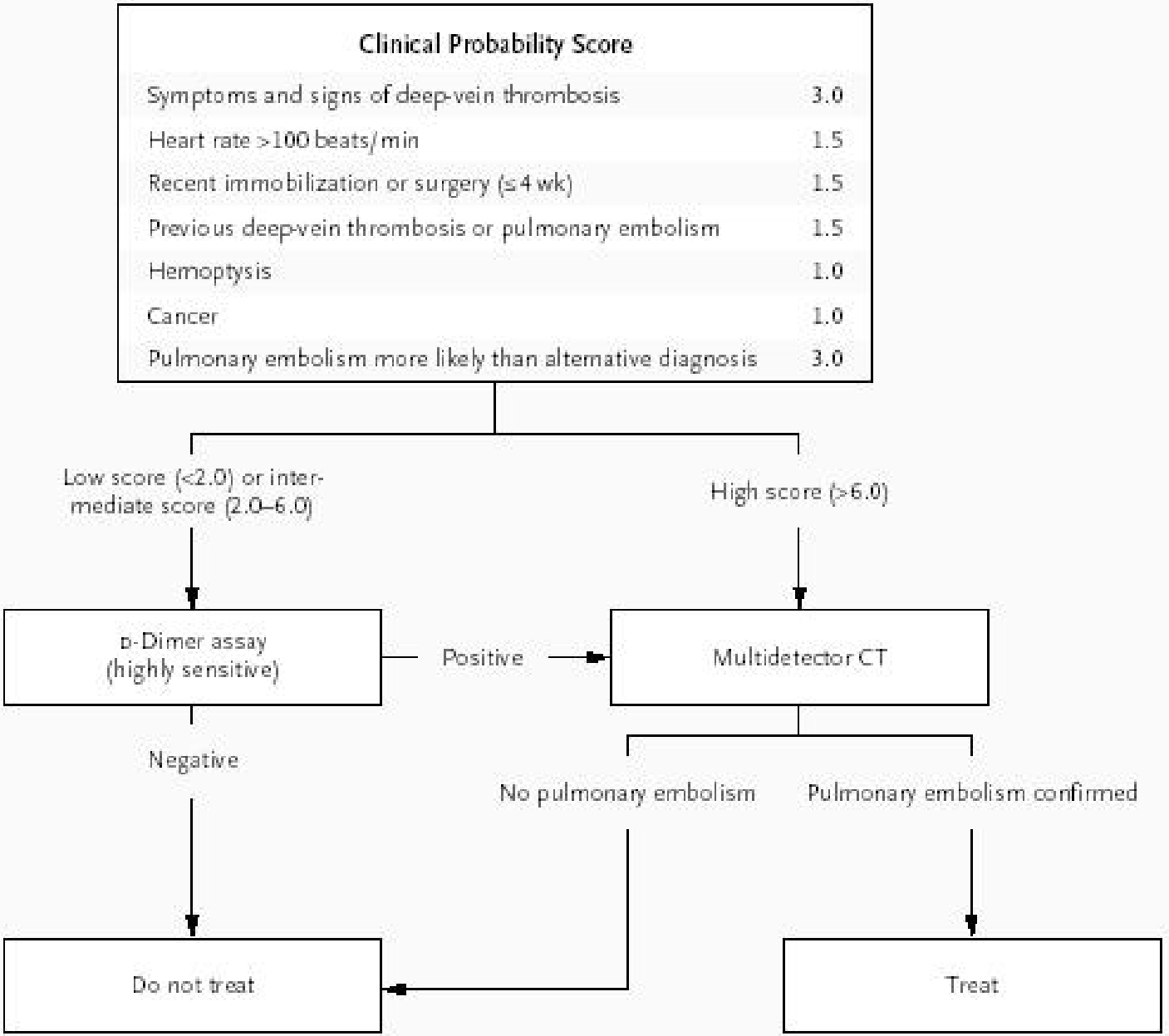


Acute Pulmonary Embolism

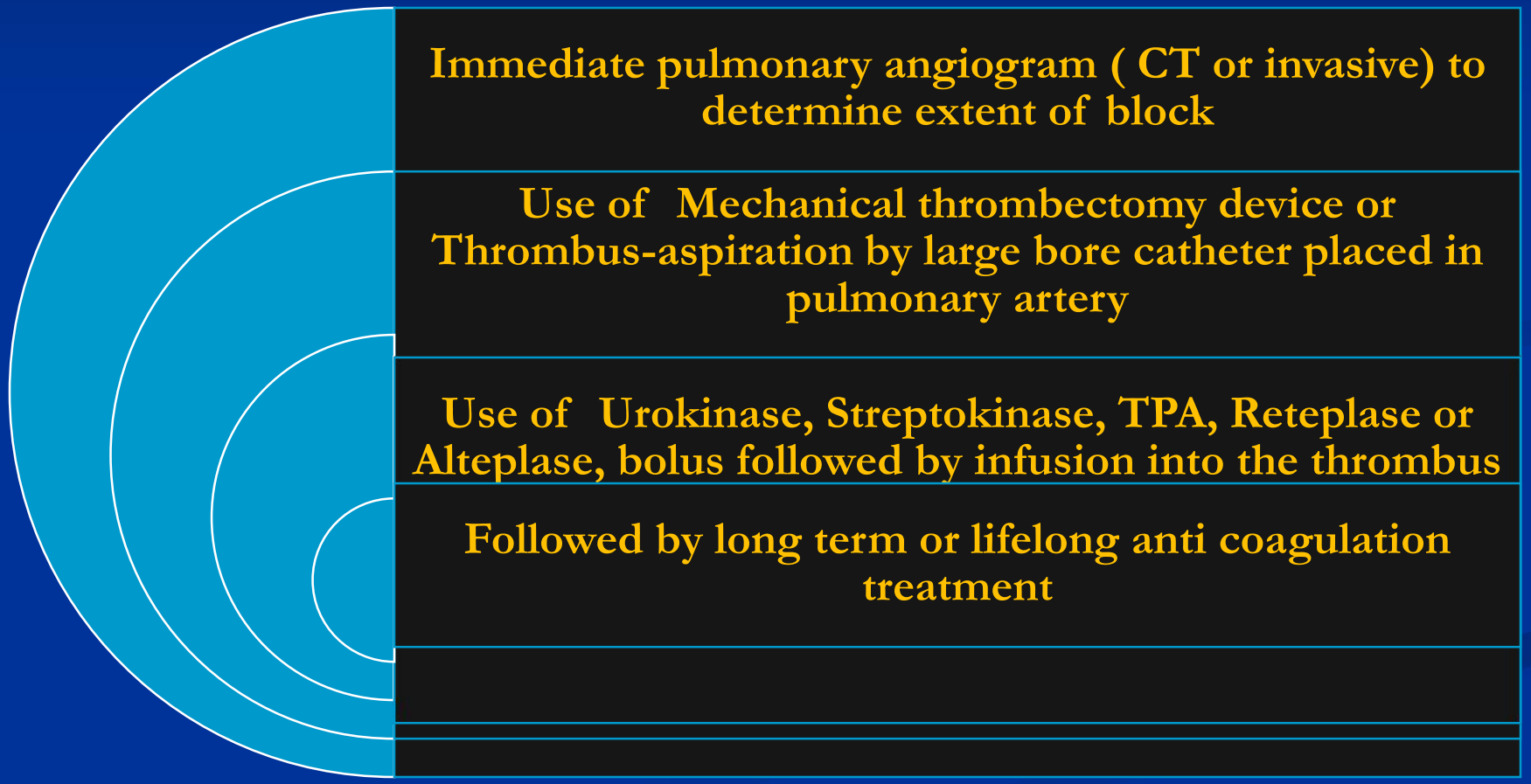







Clinical Probability Score
Symptoms and signs of deep-vein thrombosis 3.0
Heart rate >100 beats/min 1.5
Recent immobilization or surgery (≤4 wk) 1.5
Previous deep-vein thrombosis or pulmonary embolism 1.5
Hemoptysis 1.0
Cancer 1.0
Pulmonary embolism more likely than alternative diagnosis 3.0
Low score (<2.0) or intermediate score (2.0–6.0)
High score (>6.0)
D-Dimer assay (highly sensitive)
Positive
Multidetector CT
Negative
No pulmonary embolism
Pulmonary embolism confirmed
Do not treat
Treat

Treatment for Massive Pulmonary Embolism

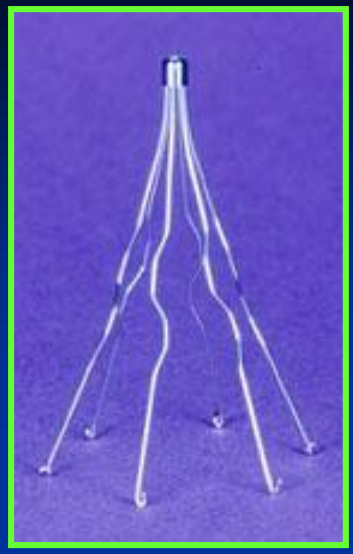


www.varicose.in

Thrombolysis for PE

www.varicose.in

Role of IVC Filter



Indications for a filter are :

severe hemorrhagic complications on anticoagulant therapy

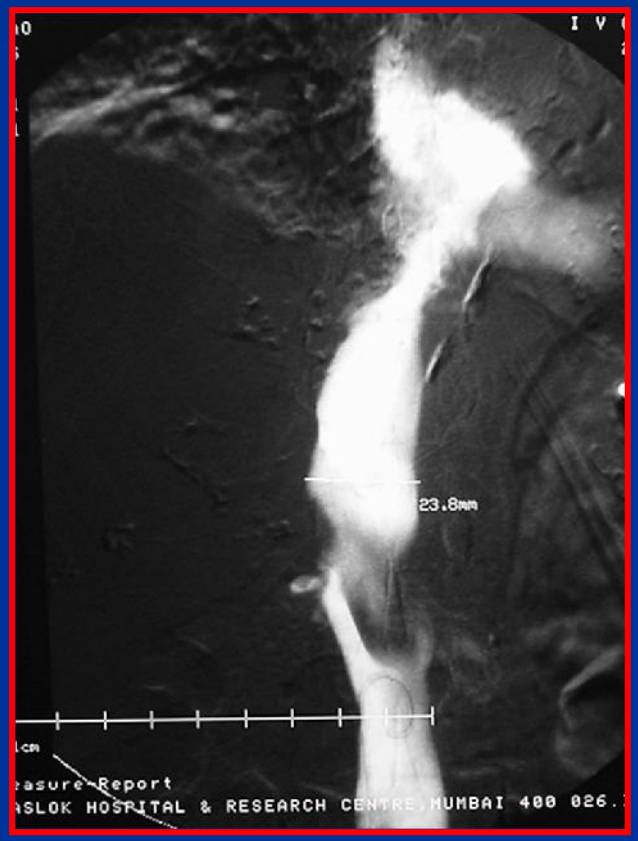
absolute contraindications to anticoagulation

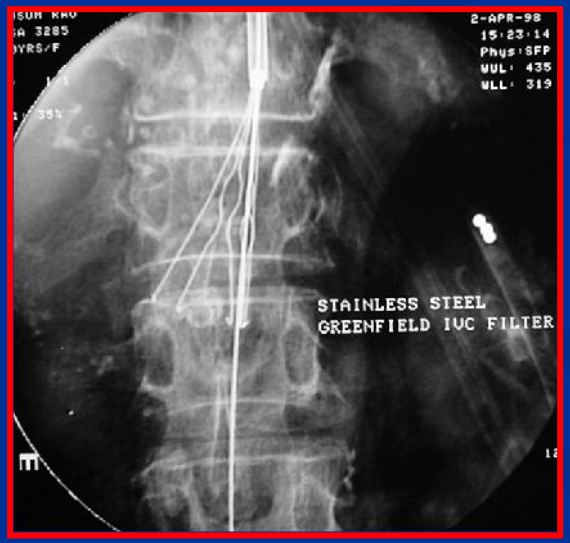
new or recurrent venous thrombosis

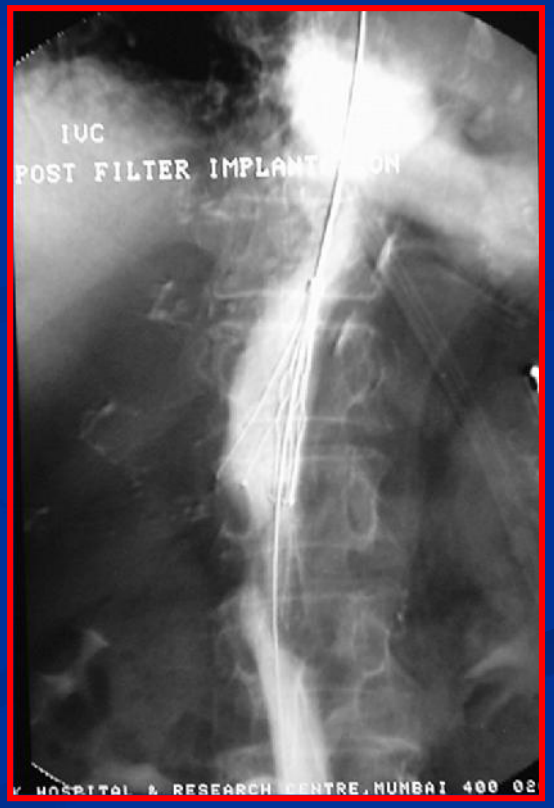
Pulmonary embolism despite adequate anticoagulation.

Treatment for Pulmonary Embolism

Placement of IVC Filter – Jugular Route

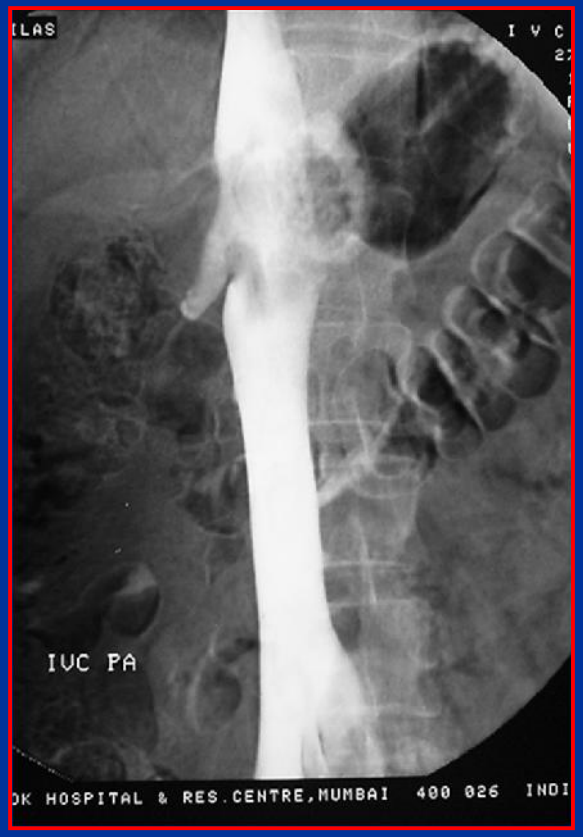


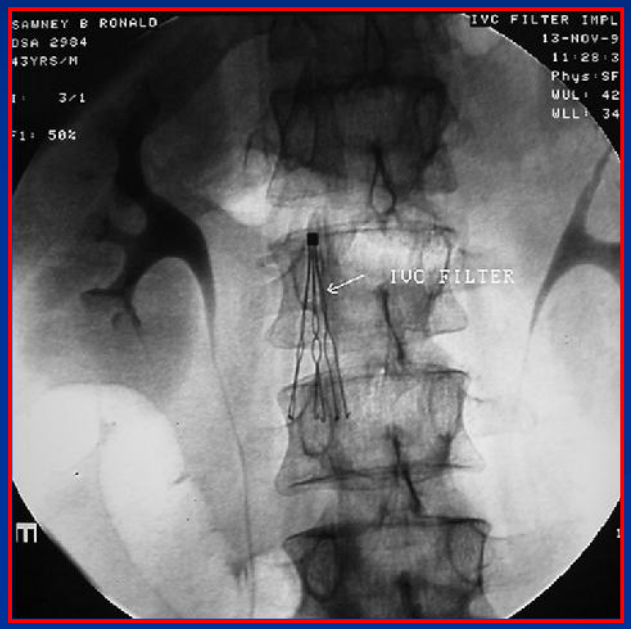


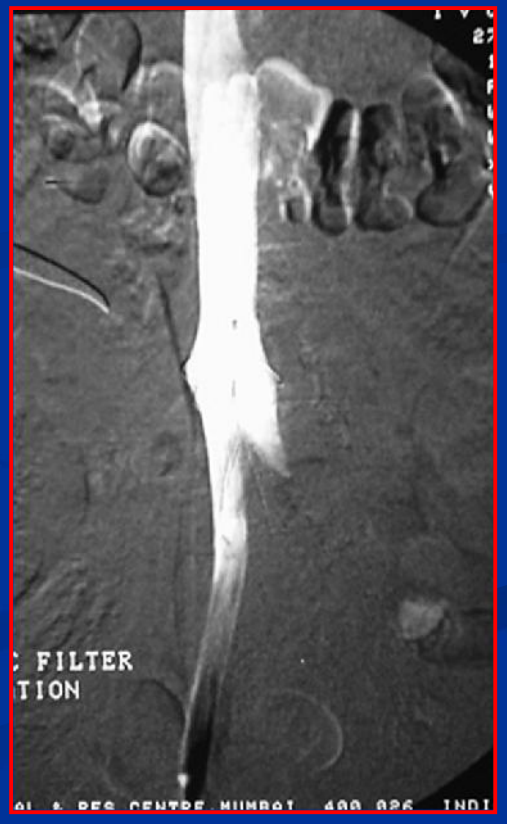


Placement of IVC Filter

Femoral Route







Delayed Complication of VTE

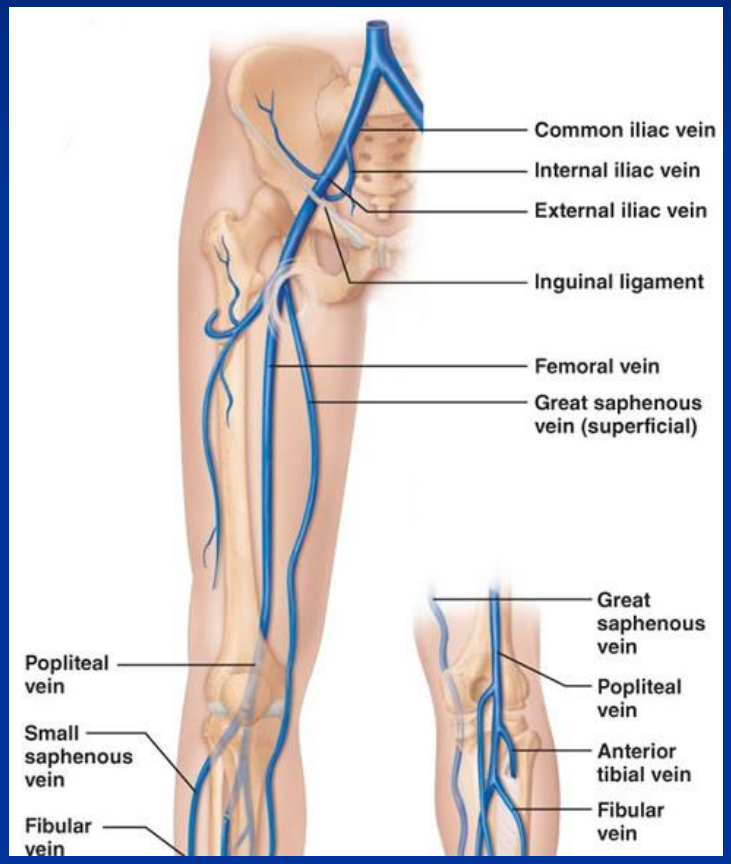
Post Thrombotic Syndrome

- Underlying cause of PTS is ambulatory venous hypertension (AVH)
- AVH is due to residual venous obstruction (Clot has not dissolved) and valvar insufficiency
- Patients with residual venous obstruction have the most severe PTS
- Most venous valves are irreparably damaged within 3 to 5 days of thrombosis

J Markel. J Vasc Surg. 15, 377-84, 1992

Ambulatory Venous Pressures and Clinical Manifestation

28 mm Hg	**Asymptomatic**
36 mm Hg	**Varicosities**
41 mm Hg	**Edema**
47 mm Hg	**Hyperpigmentation**
60 mm Hg	**Ulcer formation**



Post Thrombotic Syndrome most commonly occurs when both the Iliac and Femoral veins are blocked - Proximal DVT

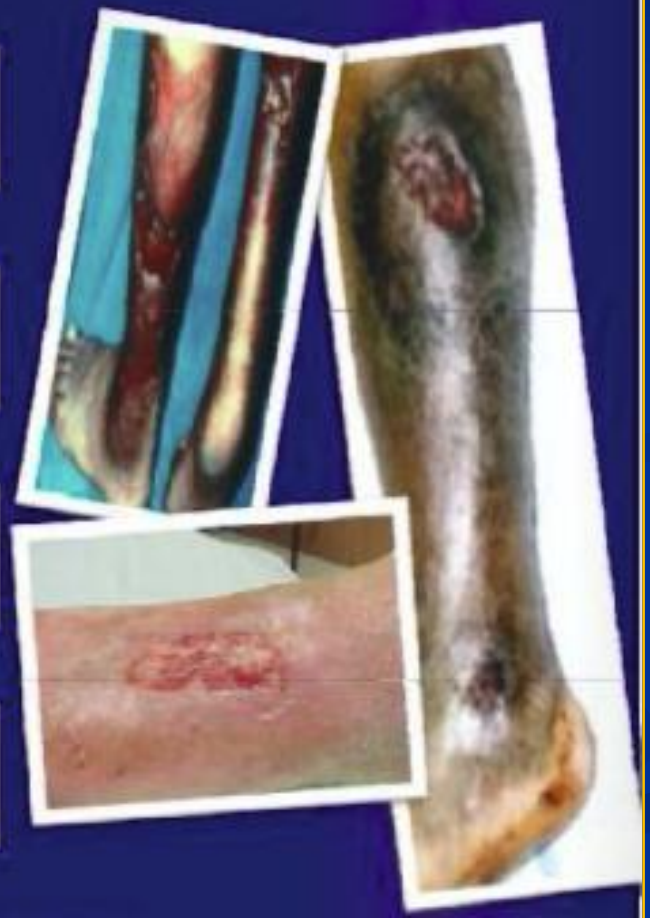
Post-Thrombotic Syndrome (PTS)
Underlying, Untreated Sequela of DVT

PTS occurs in almost half of patients within 2 years after DVT[1]

25-33% of patients with PTS develop ulcers and skin deterioration[2]

90% of patients were unable to work due to symptoms 10+ years after iliofemoral DVT[2]

PTS is a chronic condition like arthritis, chronic lung disease and angina[3]



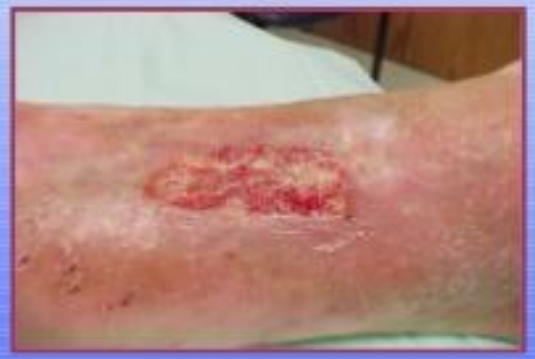
Postthrombotic Syndrome Signs & Symptoms

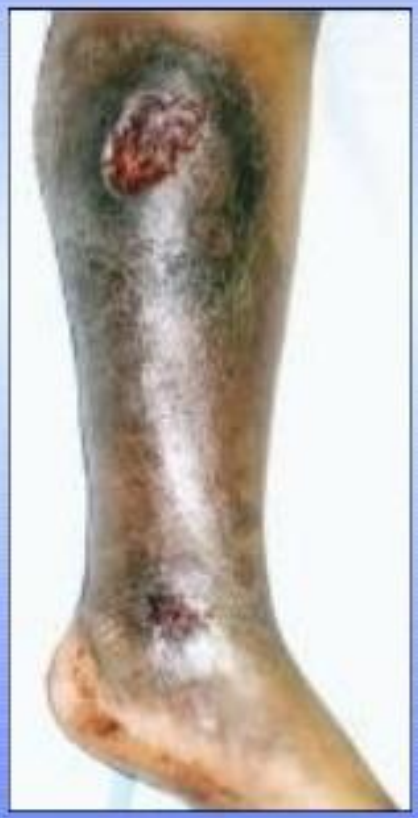
Signs

- Edema
- Stasis
- Dermatitis
- Redness
- Dependent Cyanosis
- Varicose Veins
- Venous dilation
- Open Ulcer
- Hyperpigmentation
- Healed Ulcer

Symptoms

- Heaviness
- Cramps
- Pain
- Paresthesia
- Swelling
- Bursting Pain
- Itching





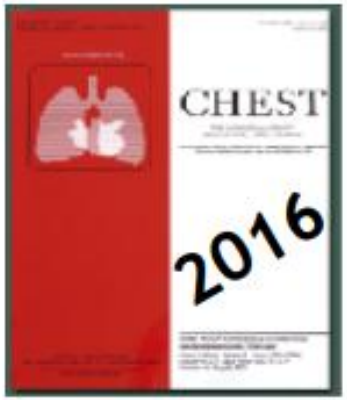
Treatment of Acute DVT

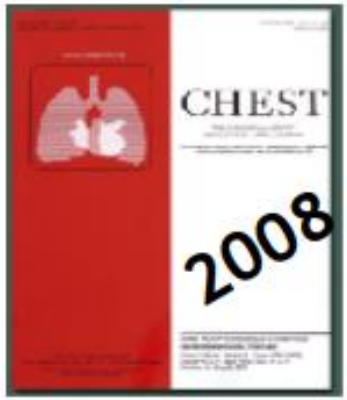
Management principles

- The goals of pharmacotherapy for DVT are to reduce morbidity, prevent post thrombotic syndrome (PTS), and prevent PE.

- Anticoagulation (mainstay of therapy) - Heparins, warfarin, factor Xa inhibitors, and various emerging anticoagulants
- Pharmacologic thrombolysis
- Endovascular and surgical interventions
- Physical measures (eg, elastic compression stockings and ambulation)

Guidelines for Treatment of VTE





UHF
LMWH
Fondaparinux
Thrombolysis

vitamin K antagonists (warfarin)

Initial treatment — INR 2.0-3.0 — 2.0 - 3.0 or 1.5-1.9

Long term-treatment

Extended* treatment

≥ 5 days — at least 3 months — indefinite*

* With re-assessment of the individual risk-benefit at periodic interval

Anti Coagulation

Helps To Prevent Formation Of New Thrombus

- Heparin therapy followed by oral anti coagulant drugs is still the mainstay of therapy
- Adequacy of initial anti coagulation is critical
  - Maintain APTT above 100. The relative risk of recurrent venous thrombo-embolism with inadequate initial heparin anticoagulation is 15:1.
- Thrombocytopenia is a known complication
  - Seen within 2 to 3 days
  - In 10-20% of patients.

(Conti S. Surgery, 92(6), 1982)

Parenteral Anticoagulation Dosing

- UFH
  - 80 U/kg IV bolus followed by 18 U/kg/hr
  - 5000U IV bolus followed by 1000 U/hr
- Enoxaparin
  - 1 mg/kg SQ Q12H
  - 1.5 mg/kg SQ QD
  - CrCl < 30: 1 mg/kg SQ Q24H
- Fondaparinux
  - < 50kg: 5mg SQ QD
  - 50-100kg: 7.5mg SQ QD
  - > 100kg: 10mg SQ QD
- Tinzaparin
  - 175 U/kg SQ QD
  - CrCl < 30: use with caution
- Nadroparin
  - 171 U/kg SQ QD
  - CrCl 30-50: reduce dose by 25-33%
  - CrCl < 30: CI
- Dalteparin – off-label

Oral Anticoagulation Therapy

- Vitamin K Antagonist - warfarin
  - Started on day 1 or 2 of parenteral anticoagulation
    - Maintain overlap for at least 5 days and INR therapeutic for 48 hours
      - INR goal = 2-3
  - Many diet, drug, and disease interactions

OR

- NOAC – rivaroxaban, apixaban, edoxaban, dabigatran
  - Preferred VTE treatment

Considerations for Using NOACs vs VKA

- Improved safety profile
- More convenient
  - In general, laboratory monitoring not required
  - Fewer drug-drug and drug-food interactions
- Bridging procedures no longer required
- An antidote is now available

Mekaj YH, et al. *Ther Clin Risk Manag*. 2015;11:967-977
Verdecchia P, et al. *Intern Emerg Med*. 2016;11:289-293

Comparison of NOAC Trials in DVT/PE Treatment: Study Designs

	XARELTO® (rivaroxaban)	ELIQUIS® (apixaban)	PRADAXA® (dabigatran)	LIXIANA® (edoxaban)
Trials	EINSTEIN DVT & PE	AMPLIFY	RECOVER I & II	HOKUSAI VTE
Sample size, n (%)	N=8282	N=5395	N=5107	N=8240
PE patients, n (%)	4832 (58)	1836 (34)	~31%	3319 (40)
Active cancer, n (%)**	430 (5.3)	143 (2.7)	~4.7%	208 (2.5)‡
Unprovoked, n (%)	5255 (63)	4845 (90)	N/A	5410 (66)
Regimen	Single oral agent concept	Single oral agent concept	Initial Heparin Bridge Required	Initial Heparin Bridge Required
Dosing	**15mg bid** x **21 d**, then **20 mg qd** [3, 6, or 12 mo]	**10 mg bid** x **7 d**, then **5 mg bid** [6 mo]	**LMWH/UFH** x **5-10 d**, then **150 mg bid** [6 mo]	**LMWH/UFH** x **5-12 d**, then **60 mg qd** [3, 6, or 12 mo]

*Postrandomization.
**At baseline.
†Double-dummy period – oral drug only, dabigatran vs warfarin.
‡HOKUSAI enrolled 771(9.3%) patients with cancer listed as the cause of DVT or PE.
For Presentation Only – Not intended for data comparison.

DVT/PE Labels: Treatment

	XARELTO® (rivaroxaban)	ELIQUIS® (apixaban)	PRADAXA® (dabigatran)	LIXIANA® (edoxaban)
Dosing	**15mg bid** x **21 d**, then **20 mg qd** [3, 6, or 12 mo]	**10 mg bid** x **7 d**, then **5 mg bid** [6 mo]	**LMWH/UFH** x **5-10 d**, then **150 mg bid** [6 mo]	**LMWH/UFH** x **5-12 d** then **60 mg qd** [3, 6, or 12 mo]
Efficacy	Noninferior	Noninferior	Noninferior	Noninferior
Major Bleeding	↓ 46%	↓ 69%	Noninferior * ↓ 40%†	Noninferior
MB/CRNMB	Noninferior	↓ 56%	↓ 38%* ↓ 44%†	↓ 19%
Renal Adjustment	Avoid if CrCL<30 mL/min	PK/PD	Avoid if CrCL<30 mL/min	30 mg qd if CrCL 30-50 mL/min Avoid if <30 mL/min

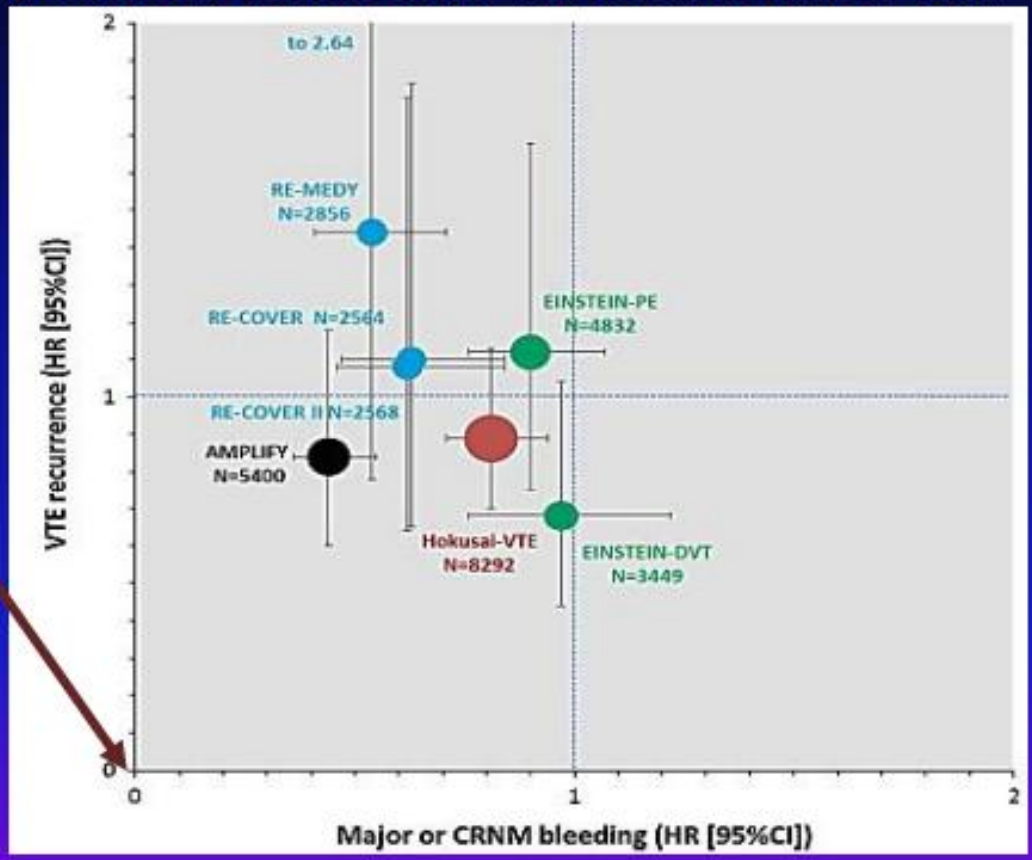
*Postrandomization.

†Double dummy period – oral drug only, dabigatran vs warfarin.

For Presentation Only – Not intended for data comparison.

Relative Comparison of DOACs

VTE recurrence and rates of major or CRNM bleeding in VTE studies that compared DOACs with either LMWH and VKAs or VKAs



Reproduced with permission from Dr Cohen. Cohen AT et al. *Adv Ther.* 2014;31:473-493.

When should you use a new oral anticoagulant?

- Your patient is adherent
- Your patient has a poor INR control (TTR < 60%)
- Your patient has good renal function (creatinine clearance 50 ml/min or better)
- Your patient has good hepatic function (AST/ALT and bilirubin normal or < 2x ULN)

When should you avoid a new oral anticoagulant?

- Your patient is poorly adherent
- Your patient has poor renal or hepatic function
- Your patient is on strong p-glycoprotein or CYP 3A4 inhibitors/inducers
- Your patient is pregnant
- Your patient is on dual anti-platelet therapy
- Your patient has cancer – probably changing

**Anti Fungals, Verapamil, Omeprazole, Erythromycin, Amiodarone, etc.

Evidence for NOACs
Newer Anti Coagulant Drugs

- 4 new RCTs and extensive clinical experience
  - Risk reduction similar between NOACs and VKA
  - Risk reduction greater with LMWH than VKA in patients with cancer
  - Risk reduction seems to be similar between all NOACs
    - No direct comparison
  - Risk of bleeding less with NOACs than VKA
    - GI bleeding may be higher, though
    - Risk may be less with apixaban
  - Risk of fatal bleeding similar between VKA and NOACs
- Conclusion, less bleeding and greater convenience with NOACs

Advantages of NOACs vs Conventional Therapy in the Secondary Prevention of VTE

Phase 3 Data for NOACs in the Extended Treatment of VTE[a]

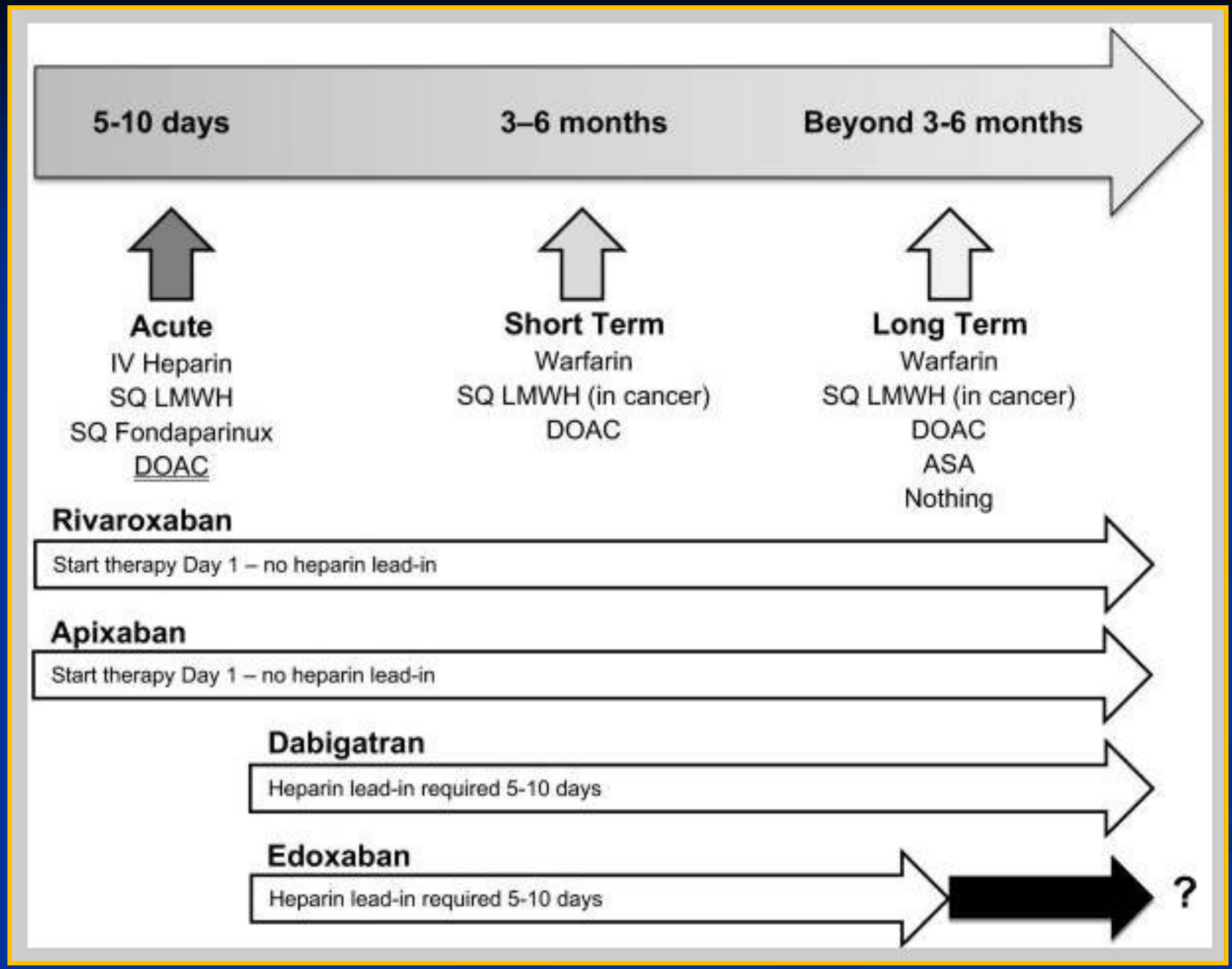
	RE-MEDY	RE-SONATE	AMPLIFY-EXT	EINSTEIN EXT
Drug	Dabigatran	Dabigatran	Apixaban	Rivaroxaban
Number of patients randomly assigned	2866	1353	2486	1197
Regimen	Dabigatran: 150 mg BID Warfarin	Dabigatran: 150 mg BID Placebo	Apixaban 2.5 mg BID or 5 mg bid Placebo	Rivaroxaban 20 mg QD Placebo
Treatment duration	6-36 m	12 m	12 m	6 or 12 m
Results for primary efficacy outcome with study drug	Noninferior	Superior	Superior	Superior
Results for primary safety outcome with study drug	No significant increase in major bleeding	No significant increase in major bleeding	No significant increase in major bleeding	No significant increase in major bleeding

- NOACs provide simplified care, with similar or improved efficacy and safety outcomes compared with VKA or heparins[b]

a. Beyer-Westendorf J, et al. *Thromb Haemost*. 2015;113:231-246.
b. Bauersachs R. *Thromb Res*. 2016;144:12-20.

NOAC Comparison

NOAC	Parenteral needed	Weight adj	DDI	Reversal	Unique
Rivaroxaban	No	No	3A4, P-gp	No	Take with food
Apixaban	No	~ No	3A4, P-gp	No	Pregnancy B
Edoxaban	Yes	Yes	P-gp	No	CrCl > 95: avoid
Dabigatran	Yes	No	P-gp	Praxbind, dialyzable	GI upset


5-10 days
3–6 months
Beyond 3-6 months
Acute
IV Heparin
SQ LMWH
SQ Fondaparinux
DOAC
Short Term
Warfarin
SQ LMWH (in cancer)
DOAC
Long Term
Warfarin
SQ LMWH (in cancer)
DOAC
ASA
Nothing
Rivaroxaban
Start therapy Day 1 – no heparin lead-in
Apixaban
Start therapy Day 1 – no heparin lead-in
Dabigatran
Heparin lead-in required 5-10 days
Edoxaban
Heparin lead-in required 5-10 days
?

Dose recommendations for Anticoagulants

Current practice

UFH/LMWH/Fonda

↓ ≥5 days

VKA (INR 2-3) for 3-6 months

For Rivaroxaban

Rivaroxaban 15mg b.i.d

↓ 21 days

Rivaroxaban 20 mg OD for 3-6 months

For Dabigatran

UFH/LMWH/Fonda

↓ ≥5 days

Dabigatran etexilate 150 mg b.i.d for 3-6 months

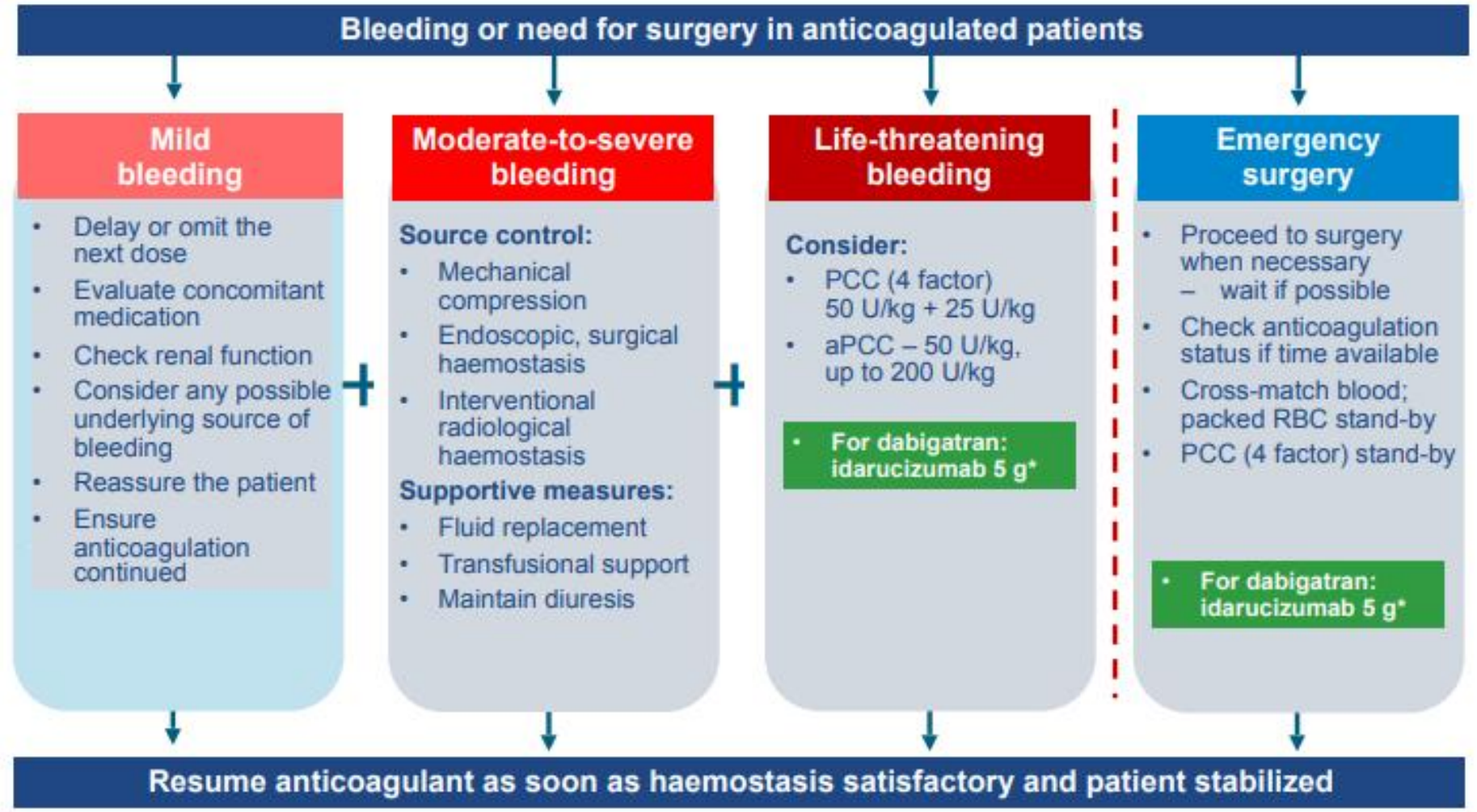
For Apixaban

Apixaban 10 mg b.i.d

↓ 7 days

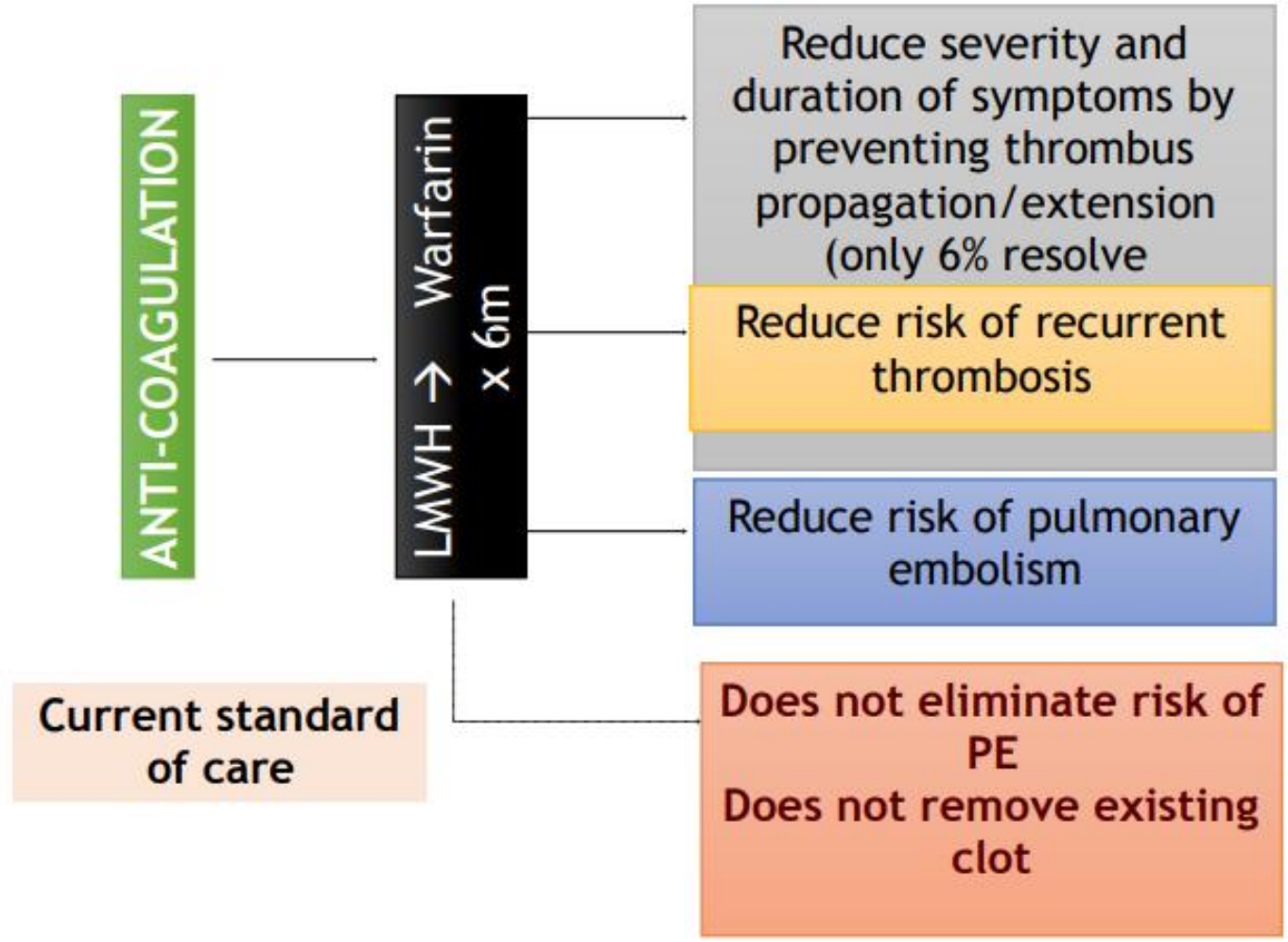
Apixaban 5 mg b.i.d for 3-6 months

Pradaxa ® SmPC 2014; Eliquis ® SmPC 2013; Xarelto ® SmPC 2013;

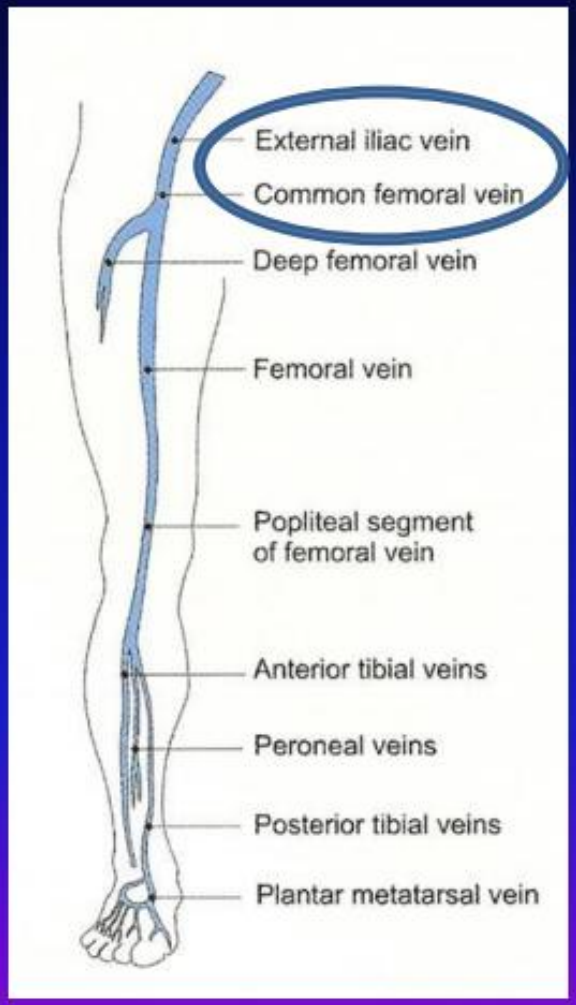

Bleeding or need for surgery in anticoagulated patients
Mild bleeding
Delay or omit the next dose
Evaluate concomitant medication
Check renal function
Consider any possible underlying source of bleeding
Reassure the patient
Ensure anticoagulation continued
Moderate-to-severe bleeding
Source control:
Mechanical compression
Endoscopic, surgical haemostasis
Interventional radiological haemostasis
Supportive measures:
Fluid replacement
Transfusional support
Maintain diuresis
Life-threatening bleeding
Consider:
PCC (4 factor) 50 U/kg + 25 U/kg
aPCC – 50 U/kg, up to 200 U/kg
For dabigatran: idarucizumab 5 g*
Emergency surgery
Proceed to surgery when necessary – wait if possible
Check anticoagulation status if time available
Cross-match blood; packed RBC stand-by
PCC (4 factor) stand-by
For dabigatran: idarucizumab 5 g*
Resume anticoagulant as soon as haemostasis satisfactory and patient stabilized

How effective is Anti Coagulation therapy is treating Proximal DVT with large thrombus burden ?

Acute DVT – why do we need intervention



Iliofemoral Venous Thrombosis



- **common femoral ± iliac** veins
- 25% of symptomatic LE DVT
- ↑ PTS
- ↑ recurrent VTE 2.4x

PMID: 21722789, 19017588, 11343664

Anti Coagulation vs. Thrombolytic Therapy in Proximal DVT

- Systemic IV Delivery of Thrombolytic Therapy
  - 13 Studies have compared Anticoagulation to Thrombolysis

Number	None/Worse	Partial %	Complete
Heparin 254	82	14	4
Lytic Drugs 337	37	18	45

Semin. Vasc. Surg. 5(2), 76-81, 1992

Ilio-Femoral DVT (proximal DVT)
Only Anticoagulation is not very effective

- Observations at 5 years
  - 95% Venous Insufficiency
  - 15% Venous Ulcerations
  - Venous Claudication develops in about 50%
  - Limited Ambulation in about 15%
  - Marked Hemodynamic impairment
  - Markedly reduced Quality of Life

- **Patient with ileo-femoral DVT (CFV and/or Iliac vein) develop PTS 60% of the time**

Author / year	Journal	N	2year PTS
Prandoni 1996	Ann Intern Med	355	23%
Brandjes 1997	Lancet	96	23%
Prandoni 2004	Ann Intern Med	90	25%
Partsch 2004	Int J Angiol	37	46%
Van Dongen 2005	J Thromb Haemost	244	30%
Kahn 2008	Ann Intern Med	387	60%
Enden 2012	Lancet	99	56%

CaVenT Trial

- Randomized, open label, 209 patients
- DVT above mid-thigh level
  - Stratified for pelvic involvement
- Intervention: CDT with rt-PA (Alteplase)
- Control: LMWH + warfarin
- Outcome:
  - Frequency of PTS (Villalta) 24 months
  - Iliofemoral patency 6 months

CaVenT Trial: 5-Year FU

	Adjunctive catheter-directed thrombolysis (n=87)		Standard treatment (n=89)		p value*	Risk difference (absolute risk reduction)
Post-thrombotic syndrome	37	42·5% (32·7–53·0)	63	70·8% (60·6–79·3)	<0·0001	28% (14–42)
Villalta severity category						
Mild (score 5–9)	31/37	83·8% (68·5–92·7)	49/63	77·8% (66·0–86·4)	..	..
Moderate (score 10–14)	2/37	5·4% (0·57–18·6)	13/63	20·6% (12·3–32·3)	..	..
Severe (score >14)	4/37	10·8% (3·7–25·3)	1/63	1·6% (0·0–9·3)	..	..
Iliofemoral patency†	68/86	79·1% (69·2–86·4)	61/86	70·9% (60·6–79·5)	0·218	−8% (−21 to 5)
Femoropopliteal reflux	54/87	62·1% (51·6–71·6)	75/89	84·3% (75·2–90·5)	<0·0004	22% (10–35)

Data are n, n/N, or % (95% CI), unless otherwise stated. *χ^2 test. †Four patients had inconclusive iliofemoral patency assessments at 5 years.

ACCP Guidelines 2016

- 16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

"…patients who are most likely to benefit from CDT have **iliofemoral** DVT, symptoms for < 14 days, good functional status, life expectancy of ≥ 1 year, and a low risk of bleeding."

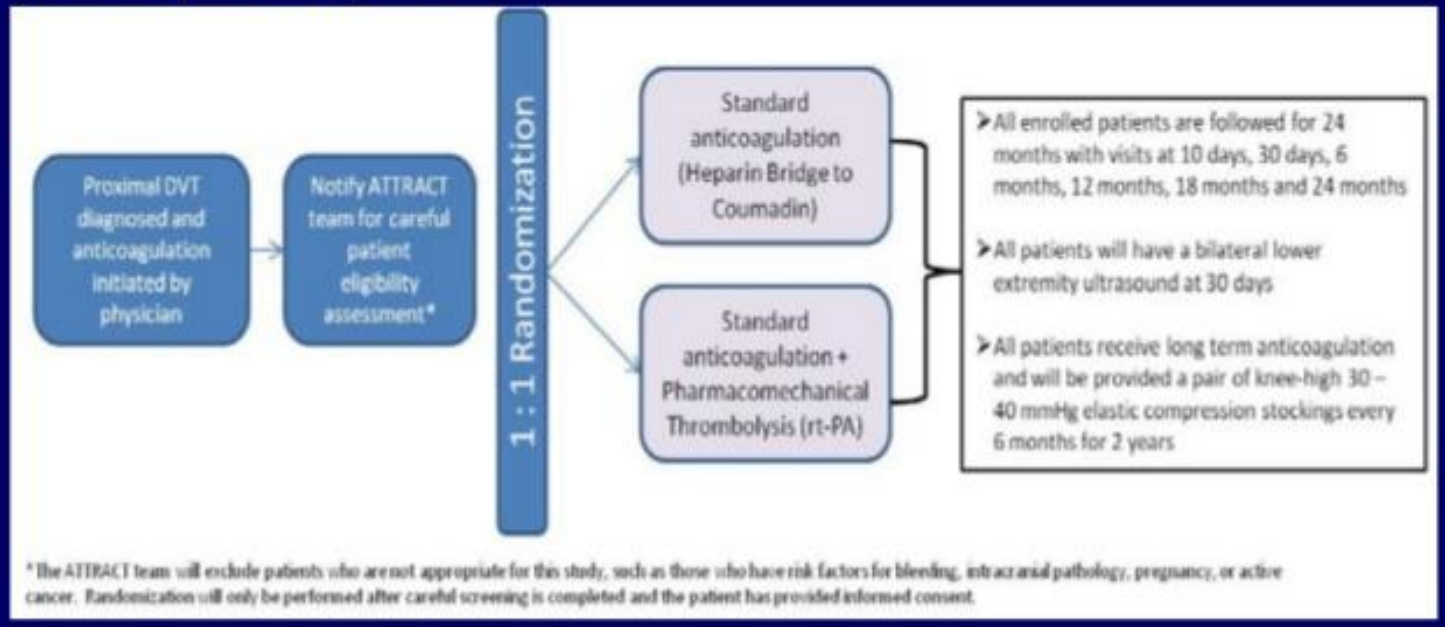
2012	2016
In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over catheter-directed thrombolysis (CDT) (Grade 2C)**.**	**In patients with acute proximal DVT of the leg, recommend anticoagulant therapy alone over catheter-directed thrombolysis (Grade 2C).**

- **Does immediate clot removal speed symptom relief, save valves, preserve patency and prevent PTS?**

Single- Centre RCTs	Multicentre RCT - CaVenT Study
❖ A 35-patient RCT found CDT with streptokinase to provide better 6-month venous patency (72% vs 12%, p < 0.01) and less valvular reflux (11% vs 41%, p = 0.042) – *Elsharawy M et al. Eur J Vasc Endovasc Surg 2002.* ❖ A 183-patient RCT found CDT-PCDT to reduce 6-month PTS (3.4% vs 27.2%, p < 0.001) and recurrent VTE (2.3% versus 14.8%, p = 0.003) – *Sharifi M et al. Cathet Cardiovasc Interv 2010.*	❖ 189 patients with femoral, common femoral, or iliac DVT: CDT + AC/comp vs AC/comp alone – *Enden T et al. Lancet 2012; 379:31-38* 2-year PTS was significantly reduced with use of CDT (41.1% versus 55.6% Control, p = 0.047) Limitations: sample size, used CDT (not PCDT)

the Attract STUDY

A multicentre randomized trial on **A**cute venous **T**hrombosis : **T**hrombus **R**emoval with **A**djunctive **C**atheter directed **T**hrombolysis **(ATTRACT)** trial sponsored by The National Heart Lung and Blood Institute (NHLBI),U.S.



the Attract STUDY

Catalyze additional pivotal VTE trials & encourage NIH and industry investment

the Attract STUDY

E-TRACT Extension
PI = Vedantham
Does PCDT Prevent Venous Ulcers?

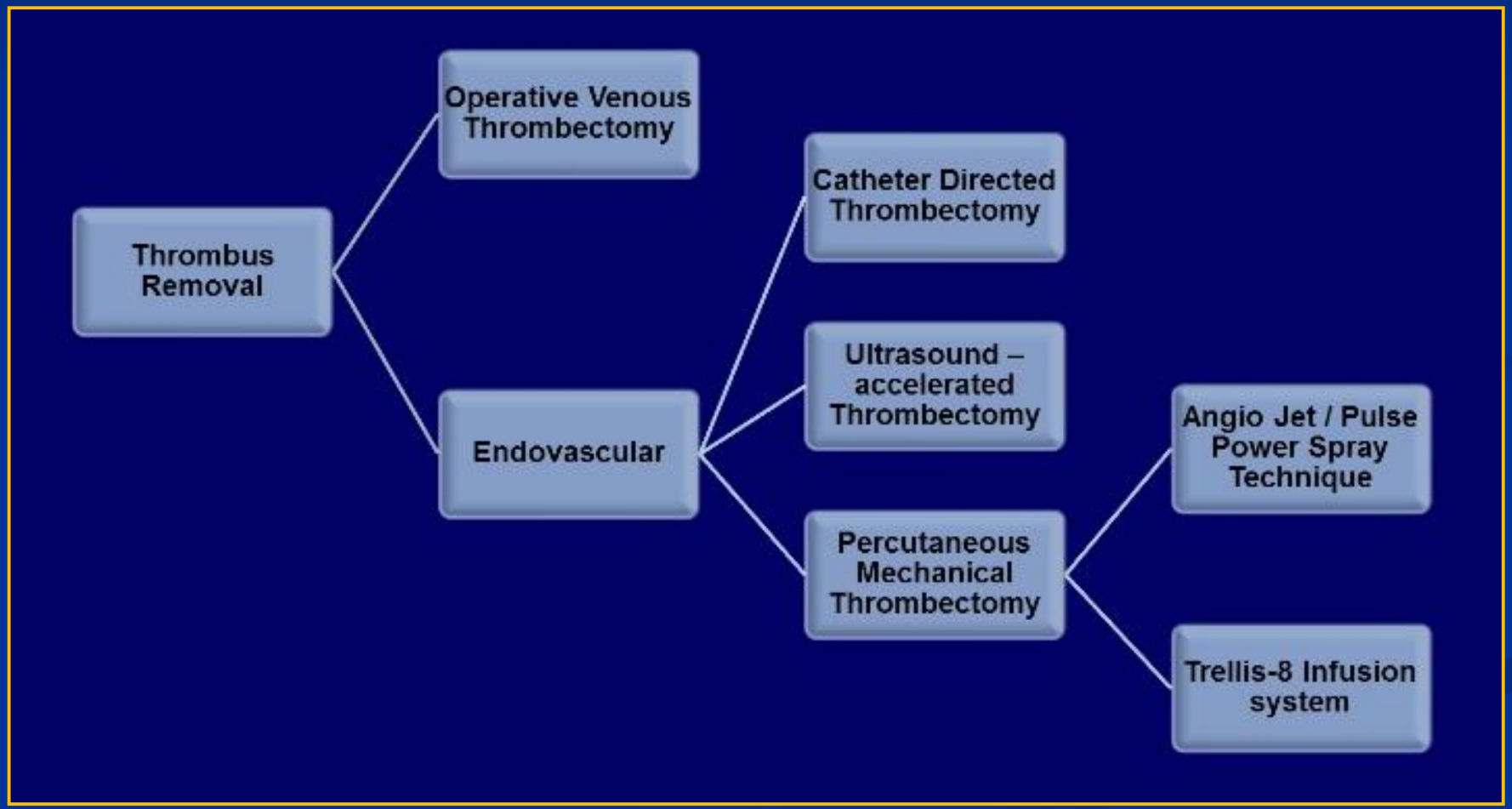
ATTRACT Vision for the Future

PHLO Study
PI = Manco-Johnson
Pediatric DVT Lysis
NHLBI Planning Grant

PE-TRACT Study
PI = Sista
CDT for Submassive PE
PCORI Letter of Intent

C-TRACT Study
PI = Vedantham
Treat Established PTS
NHLBI Planning Grant

Methods of Removal of Thrombus in Proximal DVT



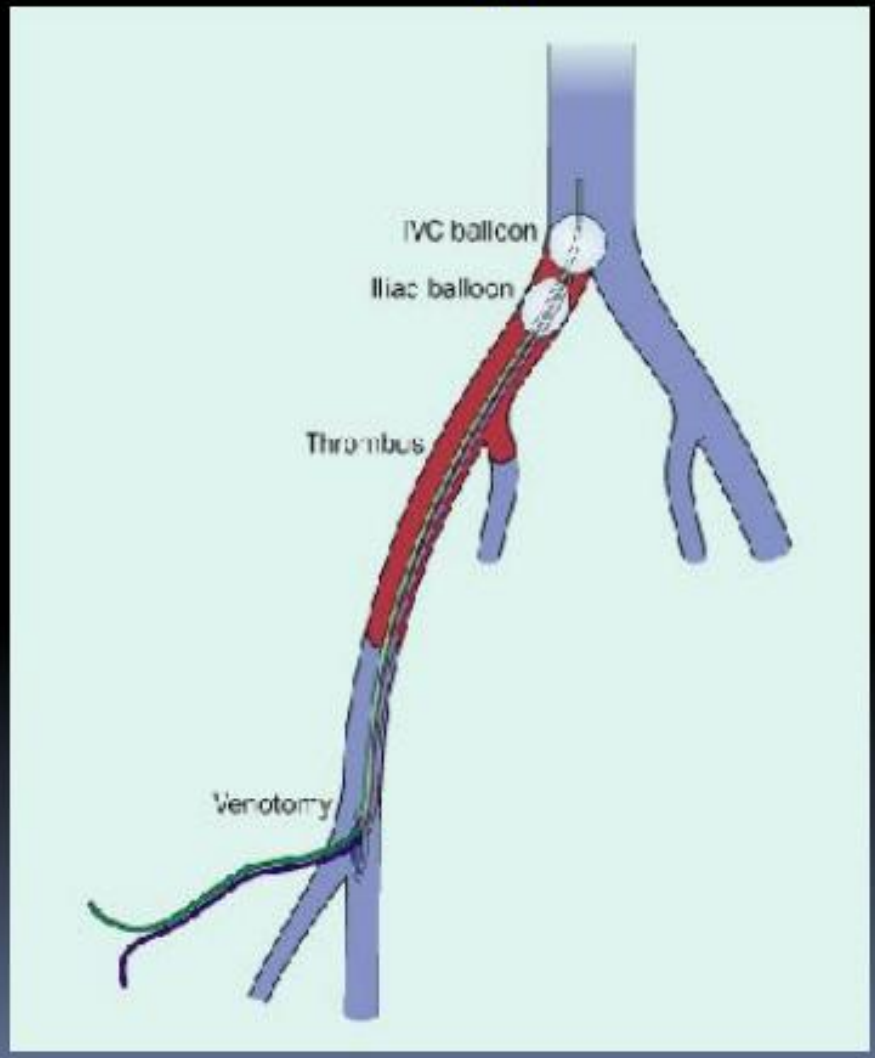
Surgical thrombectomy

•Percutaneous venous thrombectomy
Not to be done

•Open venous thrombectomy
- ***symptoms for < 7 days***
- ***good functional* status**
- **life expectancy > 1 year**

(Grade 2B)

No high risk of bleeding, we suggest that CDT is usually preferable
(Grade 2C)



Ultrasound Accelerated Thrombolysis

- In combination with CDT
- Does not directly macerate the clot
- Create micro streams, increase thrombus permeability results in augmented lytic dispersion within the thrombus.
- Parikh et al reported their initial experience with EKOS Endo wave system accelerated thrombolysis in 53 patients. Complete lysis (>90%)was observed in 70%, overall in 91%, median infusion time was 22 hours, treatment time and the dose of lytic agents were reduced.

J Vasc Interv Radiol 2008 19:521-528

Trellis-8 Infusion System

- The double balloon catheter is inserted into the thrombosed venous segment with the proximal balloon positioned at the upper edge of the thrombus.
- Balloons are inflated and rtPA is infused into the thrombosed segment isolated by the balloons.
- The intervening catheter spins at 1500 rpm for 15-20 mins.
- The liquefied and fragmented thrombus is aspirated.
- Success evaluated by repeats segmental phlebography

Angio Jet / Pulse Power Spray

The Angio Jet catheter system is comprised of a single – use catheter, single use pump set and a drive unit

Small pulses of high dose lytic agent delivered through a multi-side hole catheter with a guide wire occluding the end hole.

Jets create a localized low pressure zone at the catheter tip macerating thrombus and redirecting flow and debris into outflow channels directed behind the catheter tip for aspiration and removal.

Success in thrombus removal, restoration of venous patency, and preservation of valvular function and low haemorrhagic complications has been demonstrated.

Catheter Directed Thrombolysis

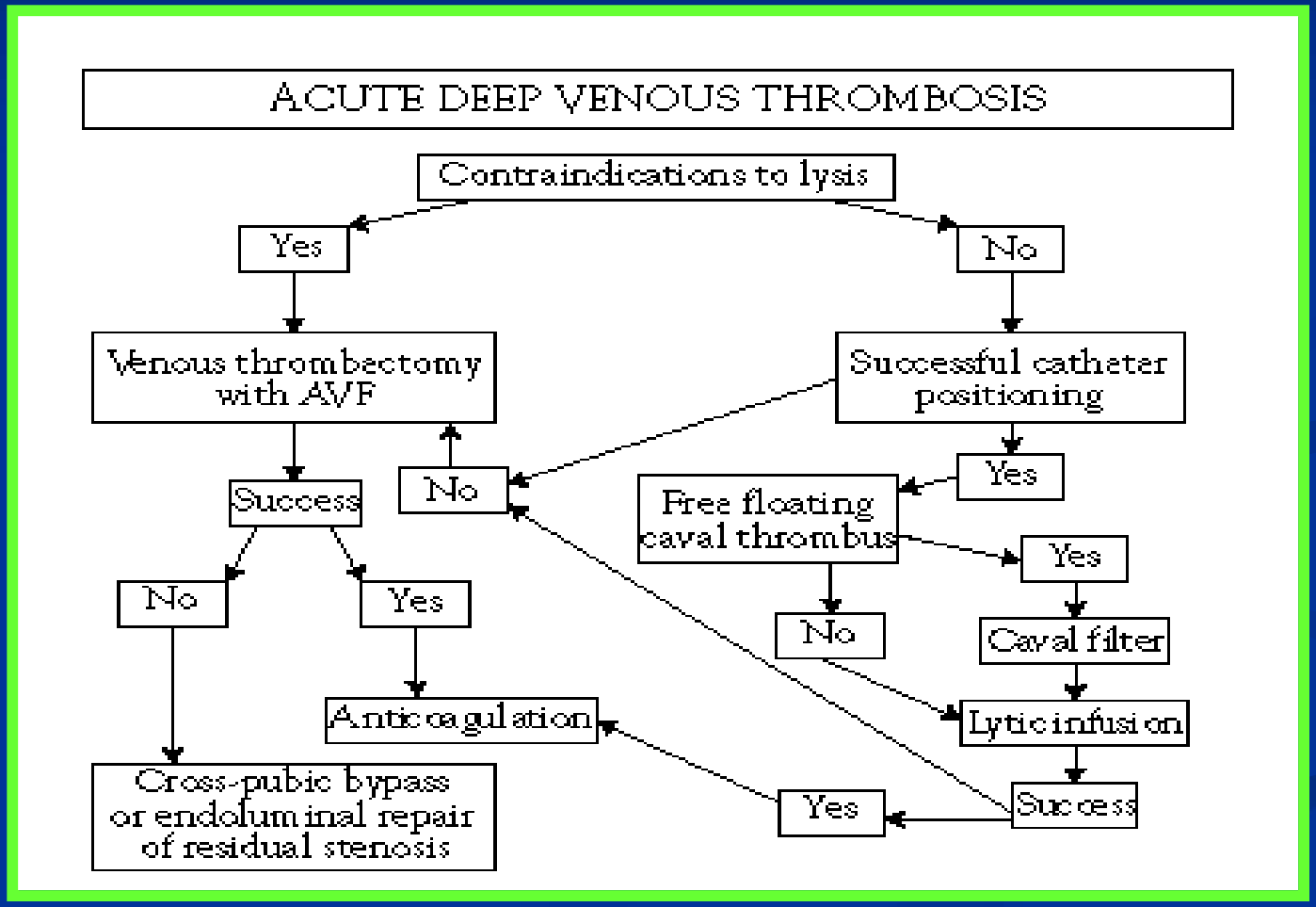
- In cath lab
- Under Local Anaesthesia
- Straight flush angio-cath with multiple sideholes
- The catheter tip is placed into the clot
- Initial lysis with rt PA 10mg diluted in 200ml NS
- Followed by rt PA infusion 1mg/hr(40 mg in 1L NS @ 25ml/hr)for 24hrs.
- In addition Heparin infusion 500 U/hr to prevent catheter thrombosis
- Monitor APTT (Therapeutic 2.5 X control) & Fibrinogen level 6hrly
- Stop infusion if Fibrinogen levels < 2mg/dl
- Ascending phlebogram before removal of catheter
- Commence full anticoagulation & Warfarin after thrombus clearance

Thrombolytic Therapy

- Long term studies over 5 years have also shown benefit of Thrombolysis
- With lysis, at 5 years , only 9% of popliteal vein valves were incompetent. Without lysis ,77% of these valves were incompetent ($p<0.001$)

Jeffrey P. Proceedings of 2nd International Vascular Symposium, London, 1986

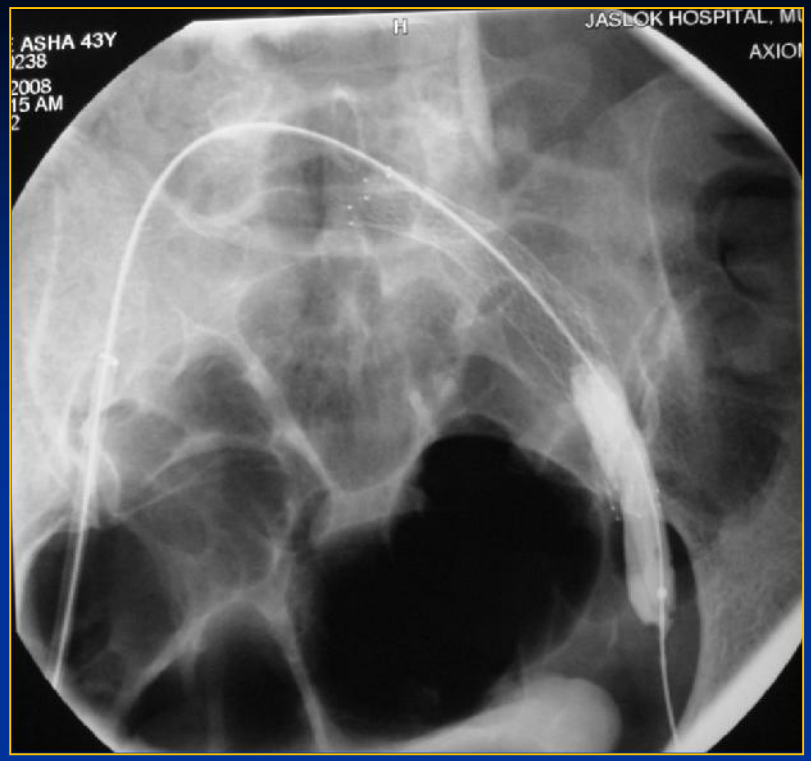
Ilio-Femoral DVT



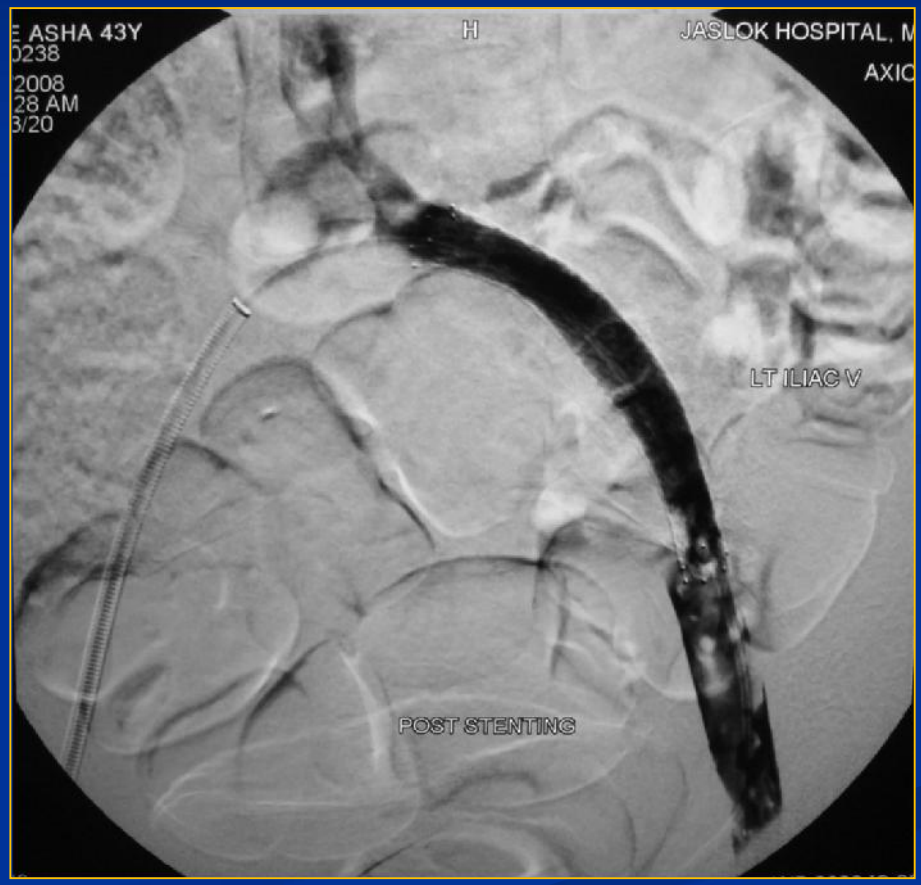
Acute DVT: Catheter Directed Thrombolysis

- 45 year old Physician
- Presented with severe swelling of the Right leg up to the groin, with pain
- 2 days history
- No response with LMWH
- Venous Doppler ultrasound examination revealed DVT of the Right Femoral and Iliac veins

www.varicose.in



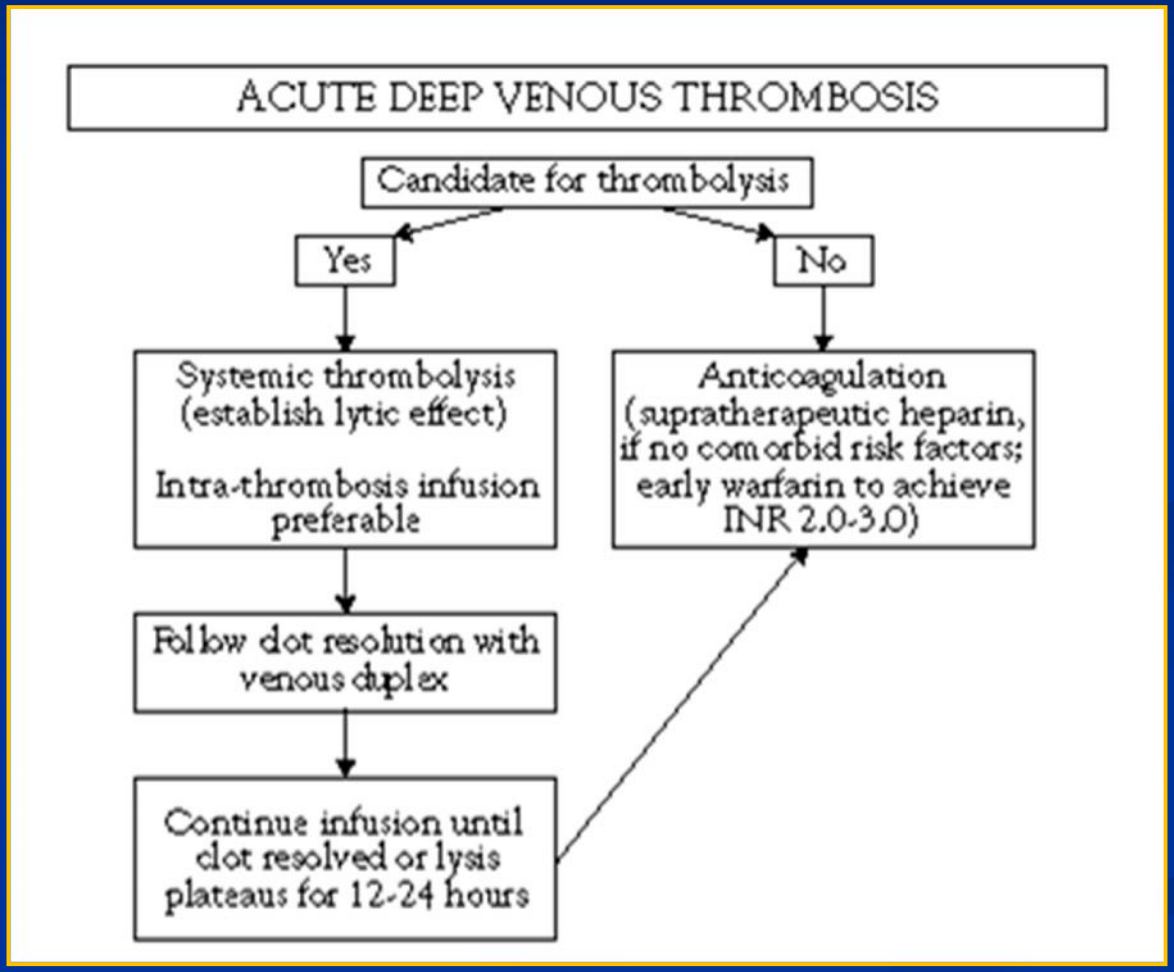
Balloon dilatation of residual stenosis



Final Result with fully open Iliac vein

Treatment Strategies for DVT

Femoro Popliteal DVT



Treatment Strategies for Distal DVT
CALF VEIN THROMBOSIS

- Thrombosis limited to calf veins – treatment is controversial
- By itself – low incidence of PE
- However, thrombi can propagate to larger veins
- Randomized trial of duration of treatment
  - 5 days of Heparin : 29% recurrence
  - 3 months of anticoagulation : No recurrence

(Lagerstadt C I . Lancet 2, 515-518, 1985)

NEW CHEST GUIDELINES

In patients with acute isolated distal DVT (IDDVT) of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

Kearon et al CHEST 2016

ISOLATED DISTAL DVT
ant/post tibeal, peroneal

TREATMENT

LOW RISK

u/s 1-2 weeks and treat only if extends proximally

HIGH RISK

treatment same as proximal DVT

HIGH RISK

- + d-dimer
- severe symptoms
- cancer
- VTE history
- no reversible provoking factor
- hospitalized
- near proximal veins
- > 5 cm long, mult veins, > 7 mm

ACCP 2016: Choice of Long Term (1st 3 Months) & Extended Anticoagulant Therapy

- **In patients with DVT of the leg or PE (w/o active cancer):**
  - **DOAC's are preferred over warfarin (Grade 2B)**
  - **Warfarin preferred over LMWH (Grade 2C)**
  - No one DOAC is preferred over the other
  - Extended treatment w/ DOACs reduces recurrent VTE and is associated with less bleeding risks

Kearon C, et al. CHEST Guideline, *Chest.* 2016.

How long to continue anti coagulation after the index episode of VTE ?

Risk of VTE Recurrence After Cessation of VTE

Risk factor	1st yr	Next 5 yrs
Distal DVT	3% (6%)	<10%
Major-transient	3%	10%
Minor-transient	5-6%	15%
Unprovoked	At least 10%	30%
Recurrent	> 10%	> 30%

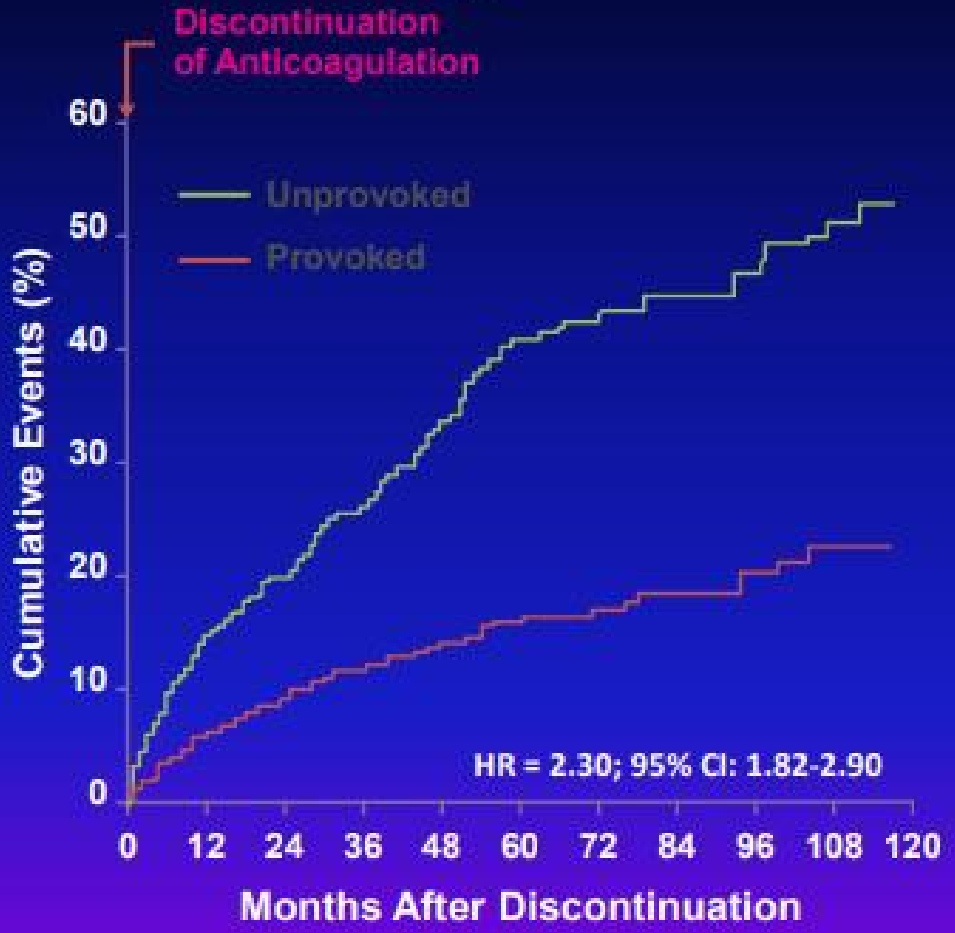
Kearon, Blood 2005

The Risk of Recurrence Is Higher With Unprovoked VTE After Discontinuation of Anticoagulation[91]

Patients with a first episode of clinically symptomatic proximal DVT and/or PE* (N=1626)

Average of 6 months of anticoagulation treatment

Patients discontinued anticoagulation and were followed for recurrent DVT/PE



*Excluded patients with active cancer, prior VTE, an indication for indefinite anticoagulation, geographic inaccessibility to follow-up, or poor life expectancy.

Clinical presentation predicts likelihood and type of recurrence

- Distal (calf vein thrombosis)
  - Low risk of recurrence/PE
- Proximal- nearly 5 fold increased recurrence risk over distal
- PE vs. DVT
  - Patients presenting with PE are 3x more likely to suffer recurrent PE than those presenting with DVT

Baglin T et al J Thromb Haemost. 2010

D-dimer and Recurrent VTE

		D-dmer +	D-dimer -
Prolong (18 months)	D-dimer @ 1 month after AC stopped	15%	6.2%
Annals 2008 (one year)	Systematic review	8.9	3.5%
Prolong II (one year)	d-dimer q 2 months after 1st negative d-dimer	27%	2.9%
Cosmi et al (18 months)	d-dimer & RVO	9-12%	0-5%

Verhovsek et al Ann Intern Med 2008;Cosmi et al Blood 2010;Palareti NEJM 2006;Cosmi Thromb Haemost 2011

Duration of AC Treatment Based on Type of VTE

Type of VTE	Recommended Duration of Treatment 2012	Recommended Duration of Treatment 2016
Proximal DVT of the leg or PE provoked by surgery	3 months	3 months
DVT of the leg or PE provoked by a nonsurgical transient risk factor	3 months	3 months
Isolated distal DVT of the leg provoked by surgery or nonsurgical transient risk factor	3 months	3 months
Unprovoked PE or DVT of the leg	At least 3 months	At least 3 months
Pt's first DVT that is an unprovoked proximal DVT of the leg or PE	At least 3 months	Extended therapy (no scheduled stop date)
In patients with a second unprovoked VTE with a low bleeding risk	Recommend extended therapy	Extended therapy (no scheduled stop date)
In patients with a second unprovoked VTE with a moderate bleeding risk	Suggest extended therapy	At least 3 months
In patients with a second unprovoked VTE with a high bleeding risk	Suggest 3 months	3 months
Patients with DVT of the leg and active cancer w/ or w/o high risk of bleeding	Extended therapy	Extended therapy (no scheduled stop date)

Aspirin for Extended Treatment of VTE

- **In patients with an unprovoked proximal DVT or PE who are stopping AC treatment and have no contraindication to aspirin, recommend aspirin over no aspirin to prevent recurrent VTE (Grade 2C).**
  - Two randomized trials have compared aspirin to placebo for the prevention of VTE in patients with a first unprovoked PE or VTE who have completed 3-18 months of AC treatment [3,4]

3. Brighton TA, et al. *The New England Journal of Medicine*. 2012. 367(21):1979-1987
4. Becattini C, et al. *The New England Journal of Medicine*. 2012. 366(21):1959-1967.

Bed rest or Ambulation

Early ambulation in preference to initial bed rest when this is feasible (Grade 1A)

Junger M et al. Curr Med Res Opin 2006; 22:593–602

Romera-Int Angiol. 2008 Dec;27(6):494-9

Is outpatient treatment safe

- LMWH at home is at least as safe as inpatient treatment for DVT
- Little evidence exists regarding outpatient treatment of pulmonary embolism

This is level 1 evidence

Use of Compression Stockings to Prevent Post-Thrombotic Syndrome

- Since the 2012 update, a larger multicenter, placebo-controlled trial found that routine use of compression stockings did not reduce the incidence of PTS or have other important benefits[7]
- This study also found that the use of compression stockings did not reduce leg pain 3 months after DVT diagnosis

7. Kahn et al. Lancet. 2014;383(9920):880-888.

2012	2016
In patients with acute symptomatic DVT of the leg, we suggest the use of compression stockings (Grade 2B)**.**	**In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS** (Grade 2B)**.**

SUMMARY

- Minimum effective duration of therapy for VTE is 3 months. If event is unprovoked consider indefinite anticoagulation if bleeding risk is low
- Add DOACS as strong evidence based options for VTE treatment
- Consider assessing individual risk benefit of extended therapy using d-dimer and clinical risk scores

SUMMARY

- Risk benefit of concomitant use of ASA plus warfarin should be assessed in each patient
- Recurrent VTE despite anticoagulation should prompt a work up for HIT, DIC, cancer, APLS MDS and requires intensification of therapy

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