

Treatment of *Thrombophlebitis*



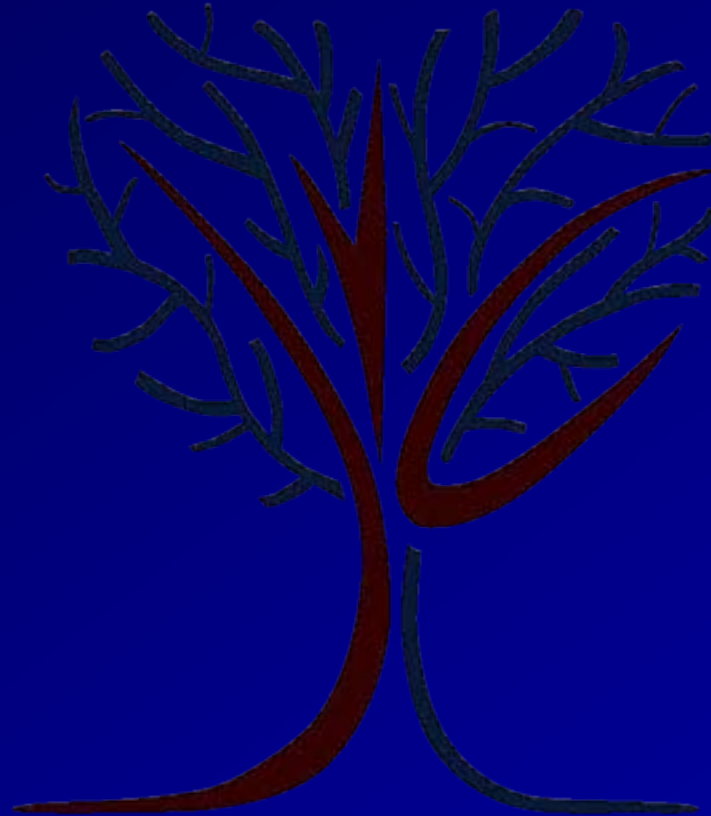
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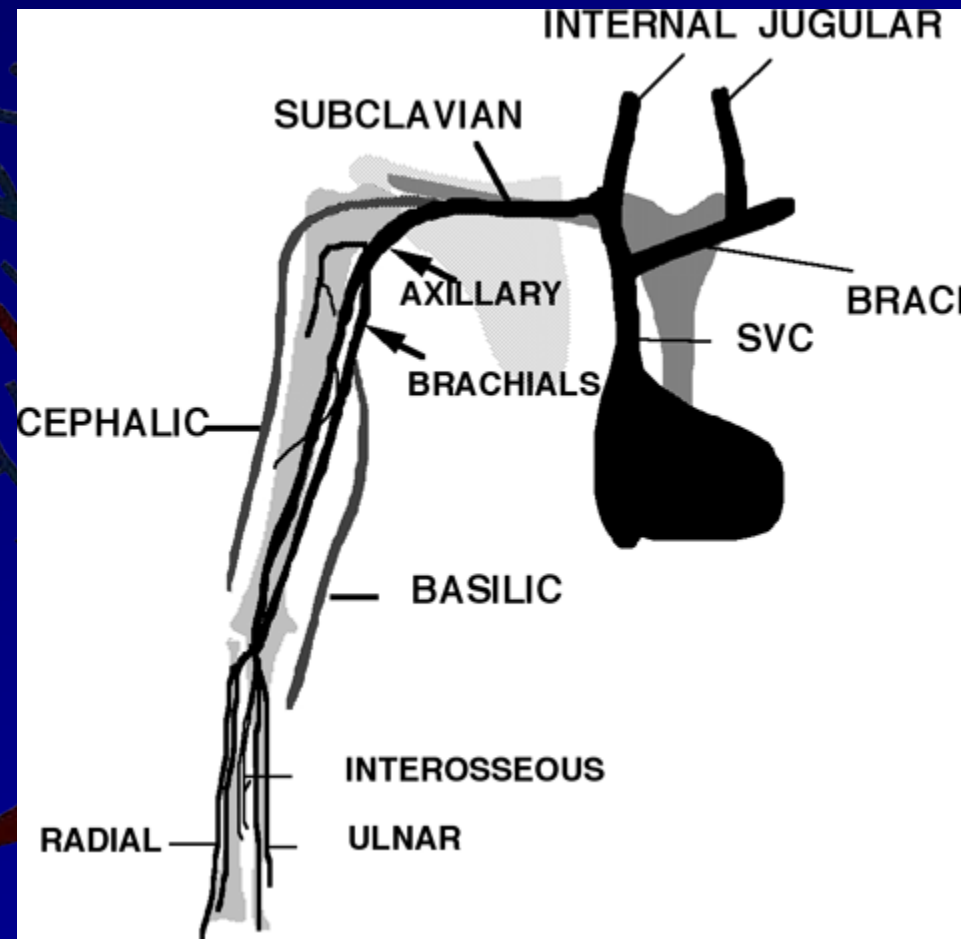
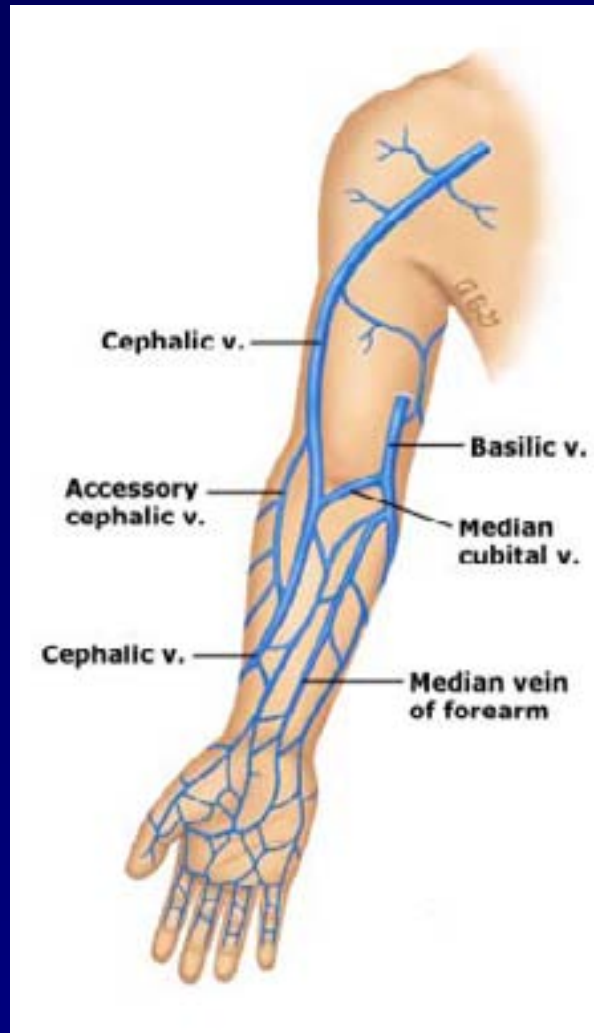
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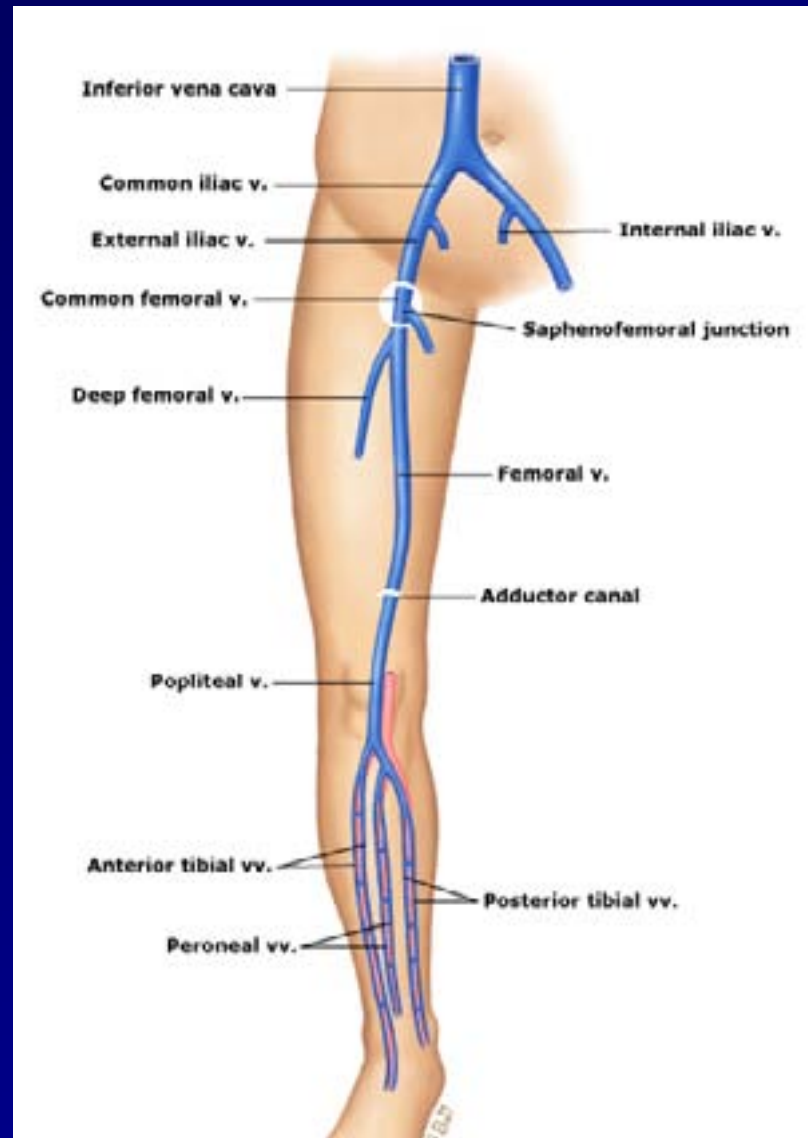
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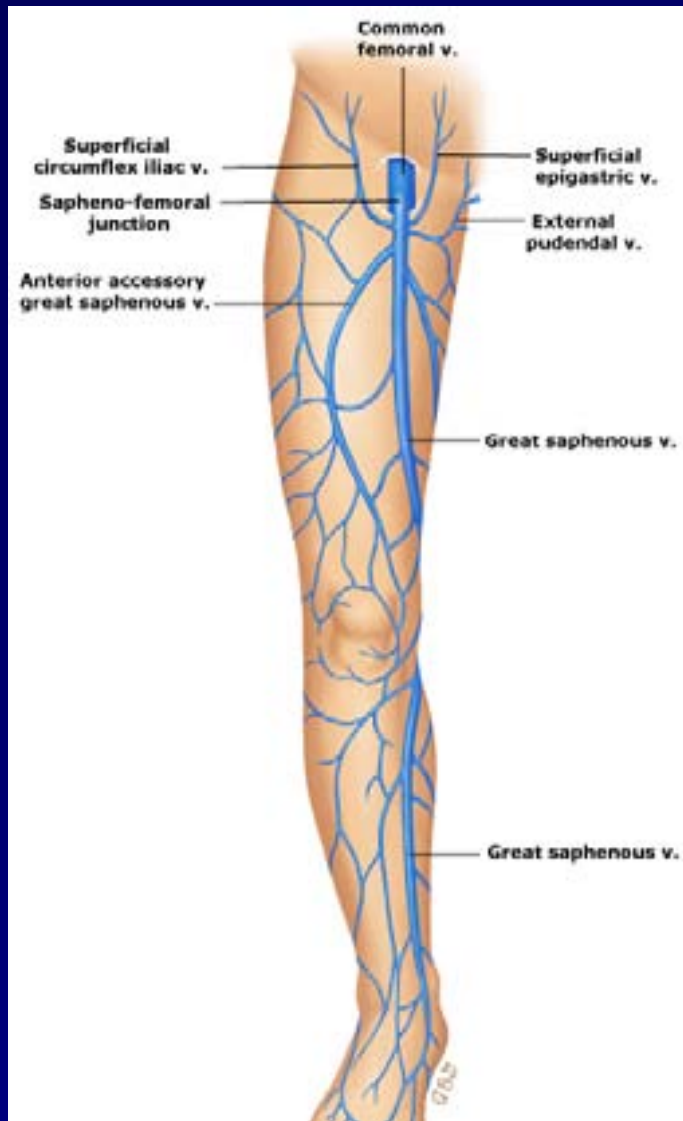
Anatomy – Upper Extremity



Anatomy – Lower Extremity Deep Veins



Anatomy – LE Superficial Veins



Pathophysiology of Venous Thrombosis

■ Virchow's Triad

– Stasis

- Immobilization

- Limb paralysis

 - (stroke, plaster cast, spinal cord injury)

- Heart failure

- Varicose vein or chronic venous insufficiency



Pathophysiology of Venous Thrombosis

■ Virchow's Triad

– Intimal injury

■ Direct vessel injury

- Surgery
- Central venous catheter
- Trauma

■ Indirect vessel injury

- Chemotherapy
- Vasculitis
- Sepsis
- Hyperhomocysteinemia



Pathophysiology of Venous Thrombosis

■ Virchow's Triad

– Hypercoagulable State

■ Hereditary

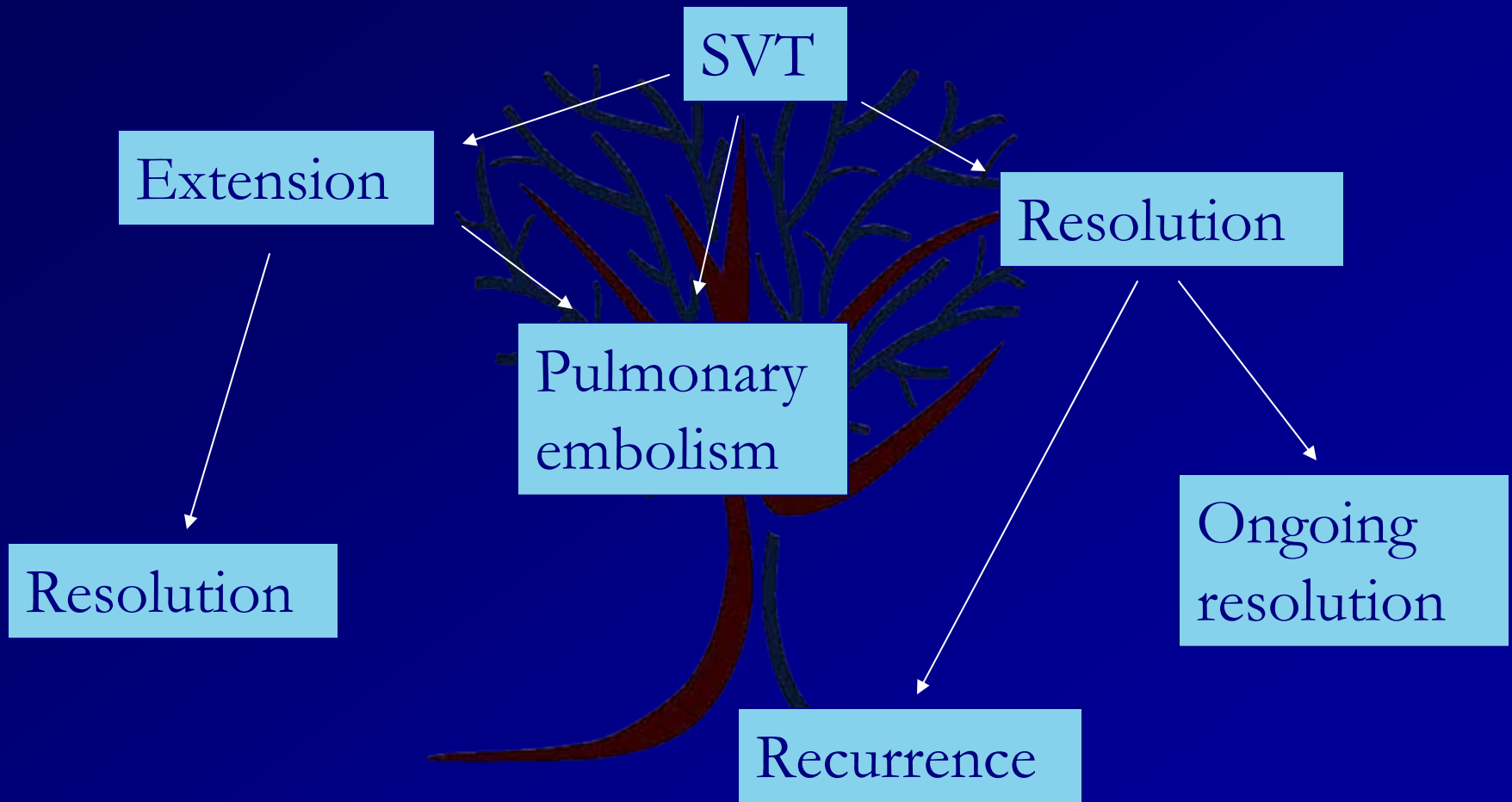
- Factor V Leiden
- Prothrombin gene mutation
- Antithrombin III deficiency
- Protein C
- Protein S

■ Acquired

- Malignancy
- Hormone replacement therapy
- Anticardiolipin antibodies
- Nephrotic syndrome



Natural History (Flowchart)



Superficial Thrombophlebitis

■ Importance

underestimated!!

■ Although it causes significant discomfort

- Benign and self-limiting

■ Literature Review

- 1-40% Progress to DVT

 - → 11%

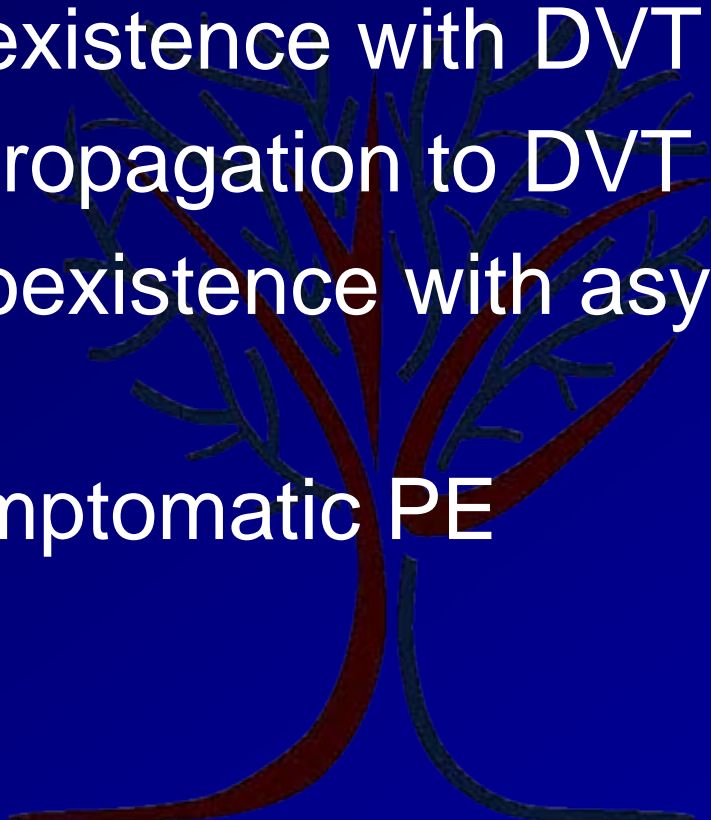
- 0-17% Progress to Pulmonary Embolus

 - → 2%



SVT Association with VTE

- 6-53% coexistence with DVT
- 2.6-15% propagation to DVT
- 20-33% coexistence with asymptomatic PE
- 2-13% symptomatic PE



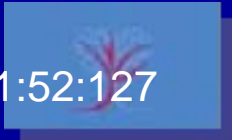
SVT and Malignancy

- Literature review looking at vascular disorders preceding a diagnosis of cancer found an association between STP and malignancy suggesting a causal link
- SVT involving the legs in 106 limbs
 - Malignancy in 14 cases (13%)
 - 3 of the 14 cancers were diagnosed after SVT
- SVT involving GSV or LSV in 398 pts
 - Ascending thrombosis in 56
 - 10 of these (18%) had malignancy



SVT and Hypercoagulability

- Association with hypercoagulable state in absence of varicose veins, autoimmune disease, malignancy
 - Factor V Leiden OR = 6
 - Prothrombin mutation OR = 4
 - Deficiency of AT, prot C, prot S OR = 13
- Anticardiolipin Ab associated with recurrent SVT
- Multiple small studies suggest an association between hypercoagulable states and SVT, especially when the saphenous trunk is involved



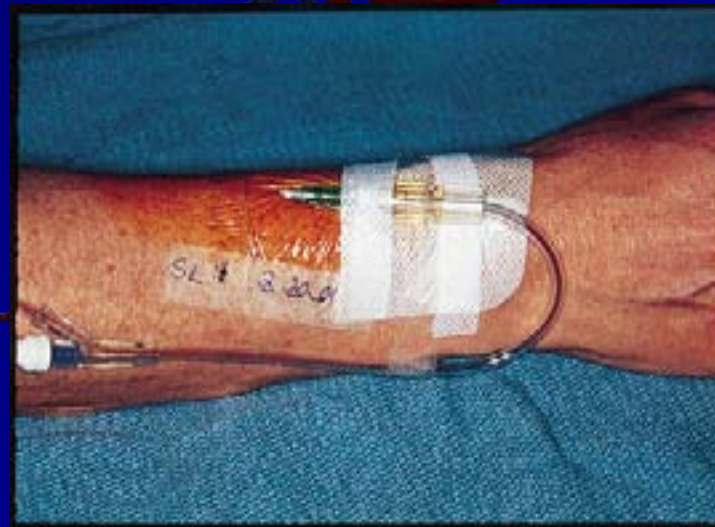
Superficial Thrombophlebitis

- Associated with Thrombophilias
 - 35%
- Associated with Varicose Veins
 - 50-93%
- All patients should undergo Duplex scanning once diagnosis suspected
 - To confirm diagnosis
 - To assess for DVT



Superficial Thrombophlebitis: *Etiology*

- Traumatic Thrombophlebitis
 - Direct injury
 - Tender cord along the course of the vein



Superficial Thrombophlebitis: *Etiology*

■ Varicose Veins

- May be antecedent to DVT
- May occur after trauma
- Most commonly due to stasis
- Presents
 - Woody induration
 - Tender hard nodule



Superficial Thrombophlebitis: *Etiology*

■ Thrombophlebitis and Infection

- DeTakats 1932, Altemeier 1969
- Potentially lethal complication
 - *S aureus*
 - *Pseudomonas*
 - *Klebsiella*
 - *Peptostreptococcus*
 - *Propionibacterium*
 - *B fragilis*
 - *Prevotella*
 - *Fusobacterium*
 - *Fusarium proliferatum*
- 1/3 cause Septicemia

– HIGH INDEX OF SUSPICION in
FUO

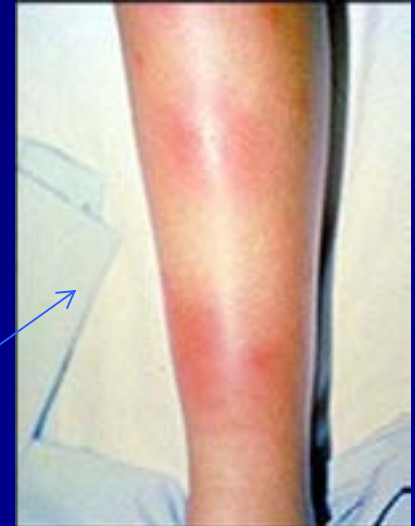


Superficial Thrombophlebitis:

Etiology

■ Migratory Thrombophlebitis

- Jadioux 1845
- Trousseau 1856
 - Trousseau's syndrome
 - Pancreatic Cancer
- Polyarteritis nodosa
- Buerger's disease
- DDX:
 - Erythema nodosum
 - Erythema induratum
 - Behcet's disease



Superficial Thrombophlebitis: *Etiology*

- Mondor's Disease: Thrombophlebitis of Superficial Veins of the Breast
 - Anterolateral portion of upper breast
 - Lower breast into epigastrium
 - Cordlike structure palpable
 - Etiologies:
 - s/p breast surgery
 - Oral contraceptive use
 - Hereditary protein C deficiency
 - Presence of anticardiolipin antibodies



Superficial Thrombophlebitis: *Etiology*

■ Unusual Forms

- Penile (Dorsal Vein) Mondor's Disease
 - Prolonged excessive intercourse
 - Hernia operations
 - Extension of Pelvic DVT



Superficial Thrombophlebitis: *Treatment*

■ Infusion Thrombophlebitis

- Diclofenac oral (75mg bid)
 - 60% vs 20% at 48h (p=0.0001)
- Diclofenac topical (tid)
 - 60% vs 20% at 48h (p=0.0001)
- Heparin gel (1000IU/g)
 - 44% vs 26% at 7 days (p=0.03)
- Essaven gel (aescinate, phospholipids, heparin)
 - 66% vs 20% at 14 days (p<0.05)



Consensus Recommendation

- For patients with symptomatic infusion thrombophlebitis as a complication of IV infusion, we suggest oral diclofenac or other NSAID, topical diclofenac gel, or heparin gel until resolution of symptoms for up to 2 weeks.
- We recommend against systemic anticoagulation.



Superficial Thrombophlebitis: *Treatment*

■ 'Simple' Thrombophlebitis

- Superficial, highly localized, mildly tender area, away from main saphenous vein
 - Aspirin and elastic support
- Associated with varicosities or when symptoms persist
 - Phlebotomy or excision of vein speeds recovery



Superficial Thrombophlebitis: *Treatment*

- 'Extensive' Thrombophlebitis
 - Severe pain, redness, brawny induration
 - Bed rest, elevation, warm wet compress



Superficial Thrombophlebitis: *Treatment*

■ 'Extensive' Thrombophlebitis

– Short Duration (8-12 days) Heparin, LMWH, NSAIDs

■ Enoxaparin 40mg SC daily

■ 8.3% @ 12days, 14.5% @ 90 days

■ Enoxaparin 1.5mg/kg SC daily

■ 5.7% @ 12 days, 15.5% @ 90 days

■ Tenoxicam 20mg PO daily

■ 13.1% @ 12 days, 15.2% @ 90 days

■ Placebo

■ 29.5% @ 12 days, 33.0% @ 90 days



NSAIDS in Addition to LMWH For Symptom Management?

- 50 pts with SVT involving the GSV randomized to therapeutic nadroparin (190 anti-Xa IU/kg qd) OR nadroparin and acetaminophen 60mg bid
- Duration of treatment 10 days
- No major complications in either group
- Significant reduction in pain and local tenderness with acetaminophen



Superficial Thrombophlebitis: *Treatment*

- 'Extensive' Thrombophlebitis
 - Longer Courses of Heparin or LMWH
 - 4 week unmonitored course in GSV thrombosis
 - 12,500 IU bid for 1 week, 10,000 bid
 - 3.3% @ 6 months
 - Low dose SC Heparin (5000 IU bid)
 - 20% @ 6 months



Consensus Recommendation

- For patients with spontaneous superficial vein thrombosis, we suggest *prophylactic or intermediate doses of LMWH* or *intermediate doses of UFH* for at least 4 weeks. As an alternative, *Vitamin K therapy* (target INR 2.5, range 2.0-3.0) can be overlapped with 5 days of UFH/LMWH and continued for 4 weeks.
- We recommend medical treatment with anticoagulants over surgical treatment.



Take Home Points

- Infusion thrombophlebitis and varicose vein thrombosis are generally benign and do not require systemic treatment
- Superficial venous thrombosis near the saphenofemoral junction has a significant risk of extension or recurrence
 - Systemic anticoagulants are generally indicated and are preferred over surgical treatment
 - Duration of therapy should probably be at least 4 weeks
 - Optimal dosing is unclear



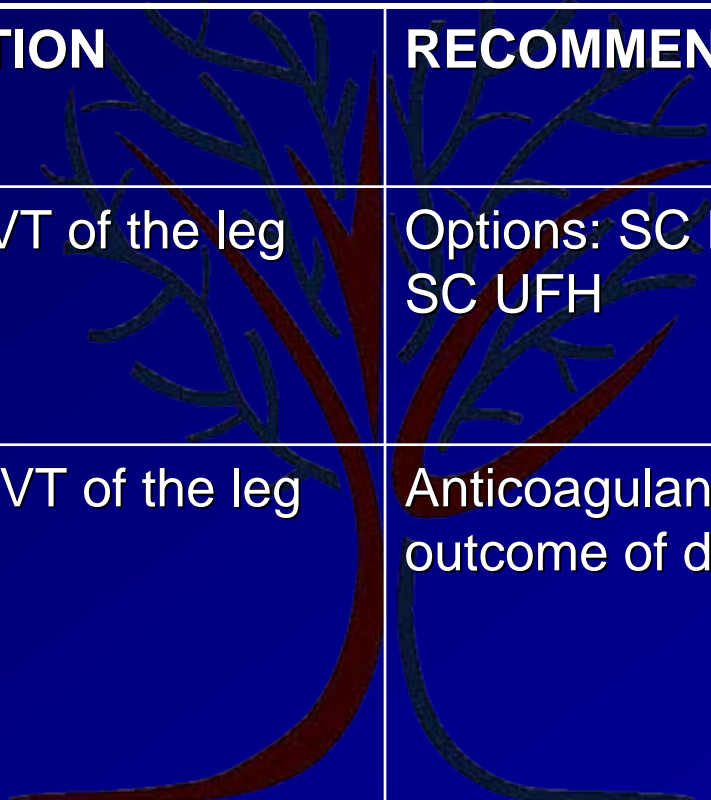
Initial Therapy for Acute DVT

- Recommend that patients receive anticoagulants as soon as the diagnosis of DVT is confirmed
- Interim treatment should be started if suspicion is high and confirmation is delayed



Guidelines for Initial Treatment

CLINICAL SITUATION	RECOMMENDED TREATMENT
Confirmed acute DVT of the leg	Options: SC LMWH, IV UFH, or SC UFH
High suspicion of DVT of the leg	Anticoagulants, while awaiting the outcome of diagnostic tests



Initial UFH or LMWH Therapy

■ IV UFH

- Continuous infusion (bolus 80U/kg or 5000U followed by initial infusion of 18U/kg/h or 1300U/h)
- Adjust dosage to prolong the APTT to a range that corresponds to a plasma heparin level of 0.3 to 0.7 IU/mL antifactor Xa activity by amidolytic antifactor Xa assay
- If therapeutic levels of APTT are not reached despite large daily doses of UFH: measure antifactor Xa levels for dosage guidance



Initial UFH or LMWH Therapy

■ SC UFH

- SC UFH is an alternative to IV UFH; initial dose 17,500 U/12h or 250U/kg/12h, then maintain the APTT within therapeutic range

■ SC LMWH

- Recommend initial treatment with SC LMWH qd or bid, over UFH, as outpatient therapy if possible, as inpatient therapy if necessary
- Recommend **against** routinely monitoring antifactor Xa levels
- Treat until INR >2.0 for 24 hours



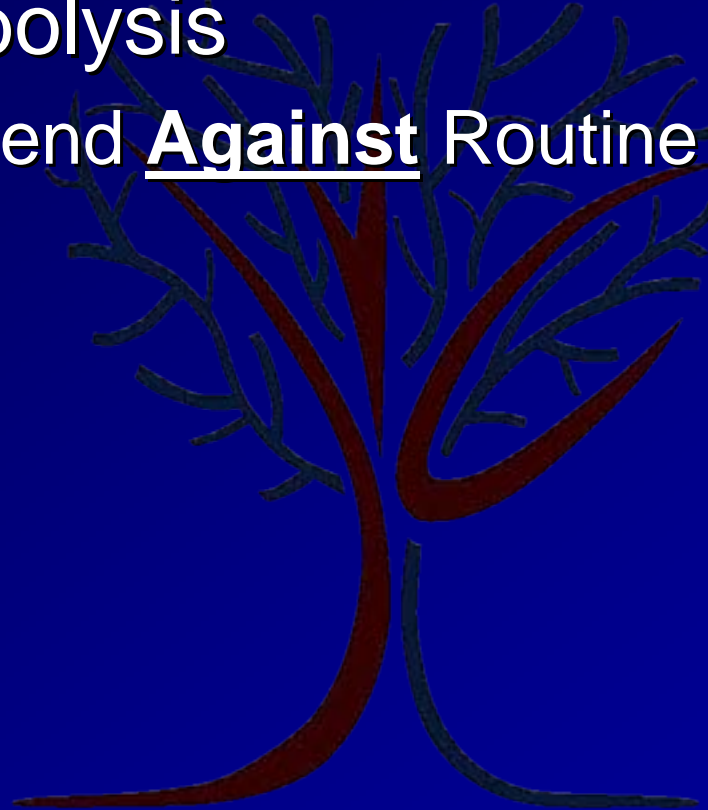
Initial Warfarin Therapy

- Starting Warfarin at a dose of 5mg, compared to 10mg, is associated with less excessive anticoagulation.
- Start at 10mg in younger (<60 years), otherwise healthy outpatients, and at 5mg in older and hospitalized patients.



Systemic Thrombolysis as Initial Therapy

- IV Thrombolysis
 - Recommend Against Routine Use



Catheter Directed Thrombolysis

- Recommended in 'Extensive Acute Proximal DVT'
 - Iliofemoral or Axillosubclavian DVT
- In 'Selected' patients
 - Symptoms for < 14 days
 - Good functional status
 - Life expectancy > 1 year
 - Low risk of bleeding
- "Can reduce symptoms and post-thrombotic morbidity if appropriate expertise is available"

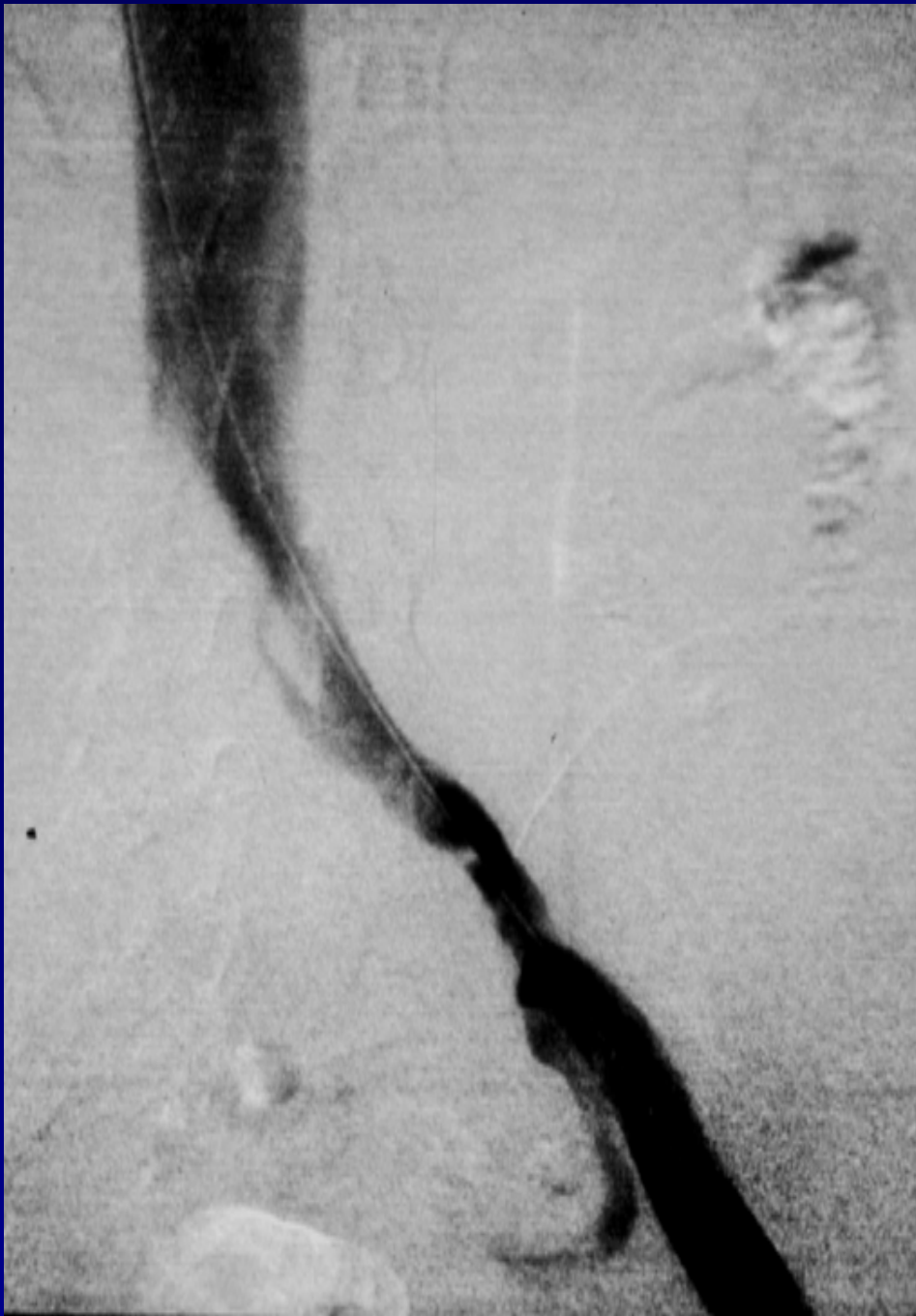


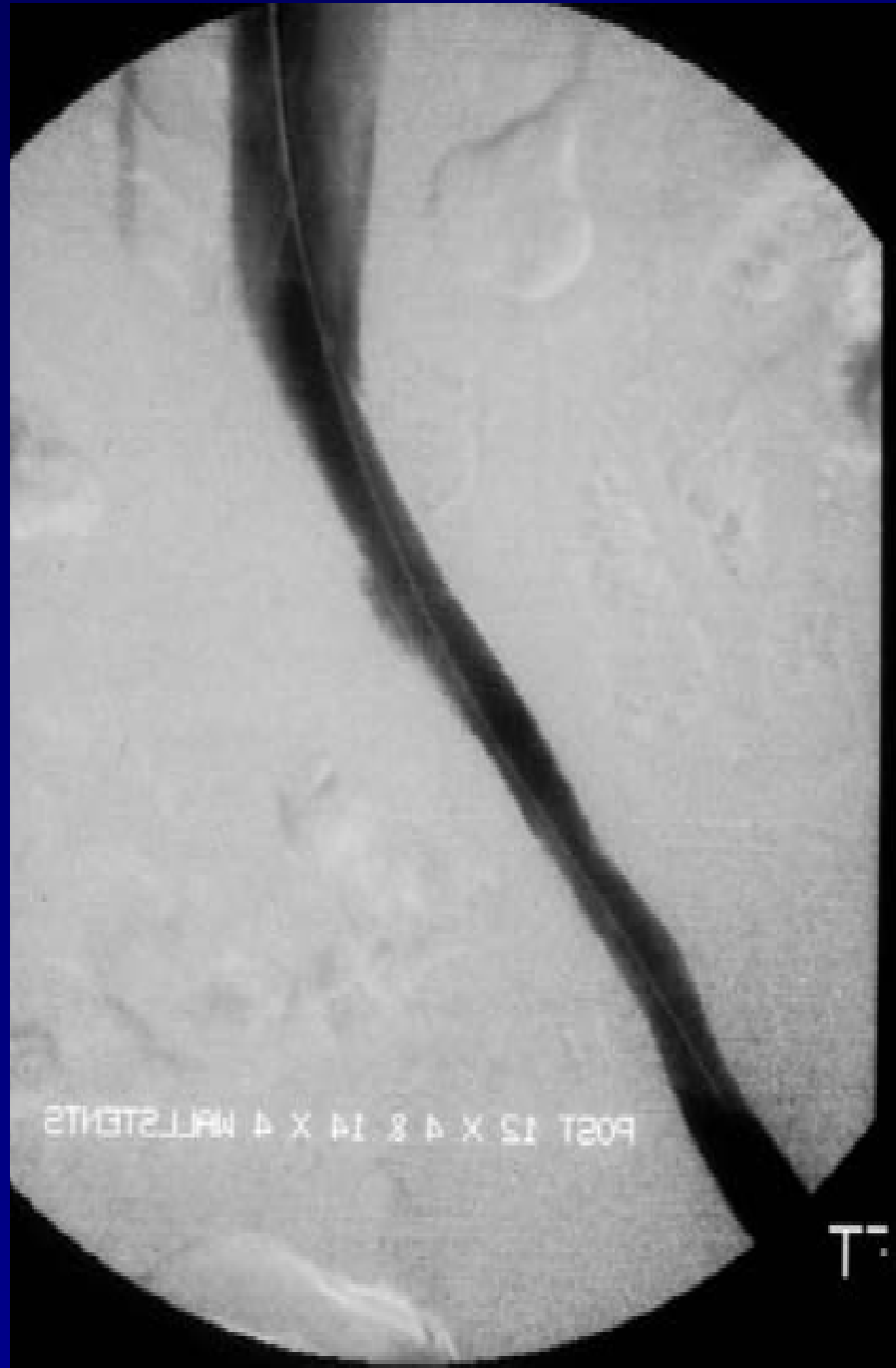
Catheter Directed Thrombolysis

- “After successful CDT, we suggest correction of underlying venous lesions using balloon angioplasty and stents.”
- Recommend pharmacomechanical (with inclusion of thrombus aspiration and/or fragmentation) thrombolysis in preference to CDT









Immobilization?

- Early Ambulation
 - When feasible



Long-term Therapy for DVT

First DVT episode, secondary to a transient (reversible) risk factor

- VKA therapy for 3 months

First episode of idiopathic DVT

– Proximal

- 6-12 months

- If no risk factors for bleeding and can monitor

 - → indefinite

– Distal

- 3 months



Risk-Stratification for 'Indefinite Therapy'

- Increases risk in unprovoked DVT
 - More than one episode – RR 1.5
 - Antiphospholipid antibody – RR 2.0
 - Hereditary thrombophilia – RR 1.5
 - Male – RR 1.5
 - Residual thrombus in vein – 1.5
- Protective
 - Calf DVT – RR 0.5
 - (-) d-dimer 1 month after stopping VKA – RR 0.4
 - Asian ethnicity – RR 0.8



Risk-Stratification for 'Indefinite Therapy'

- Increases risk of bleeding
 - Older age (esp >75)
 - Previous GI bleed (esp. if not assoc w\ rev cause)
 - Previous noncardioembolic stroke
 - Chronic kidney or liver disease
 - Concomitant antiplatelet therapy
 - Suboptimal monitoring



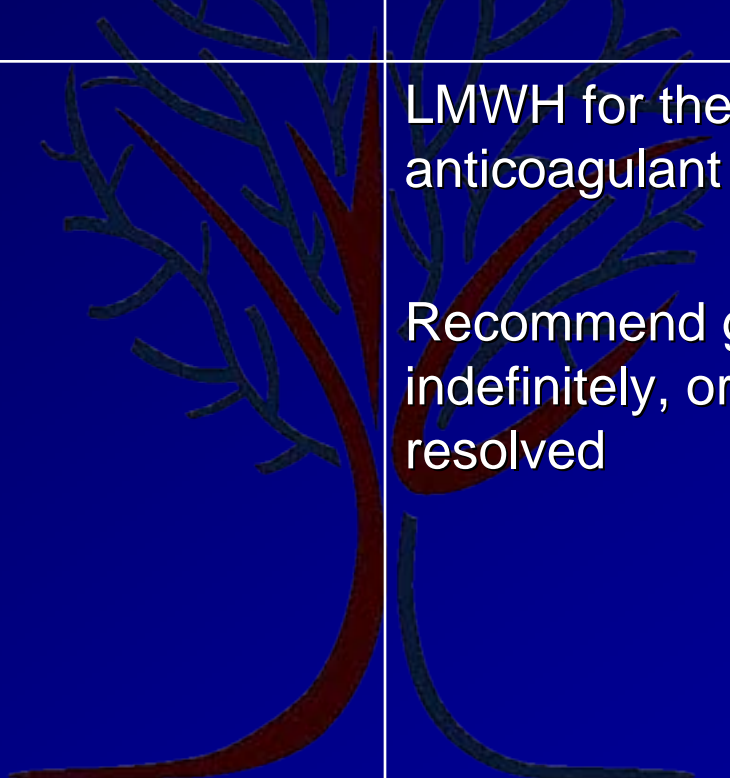
Cancer and DVT

- 11% of patients with known cancer will develop DVT/PE
- 3-5% of patients with DVT and PE unprovoked will have previously unknown diagnosis of malignancy at the time DVT is diagnosed.
- DVT/PE is the 2nd leading cause of death in those with malignancy.
- Those with DVT at the time of their cancer diagnosis are more likely to have metastasis of their cancer and have lower overall survival rate.



Cancer and DVT

PATIENT CHARACTERISTICS	RECOMMENDED TREATMENT
DVT and cancer	<p>LMWH for the first 3 to 6 months of anticoagulant therapy</p> <p>Recommend giving anticoagulants indefinitely, or until the cancer is resolved</p>



Long-term Therapy for DVT

PATIENT CHARACTERISTICS	RECOMMENDED TREATMENT
<p>First DVT episode and either documented antiphospholipid antibodies (APLAs) or two or more thrombophilic conditions, eg, combined factor V Leiden and prothrombin 20210 gene mutation</p>	<p>VKA therapy for 12 months</p> <p>Suggest giving anticoagulants indefinitely</p>

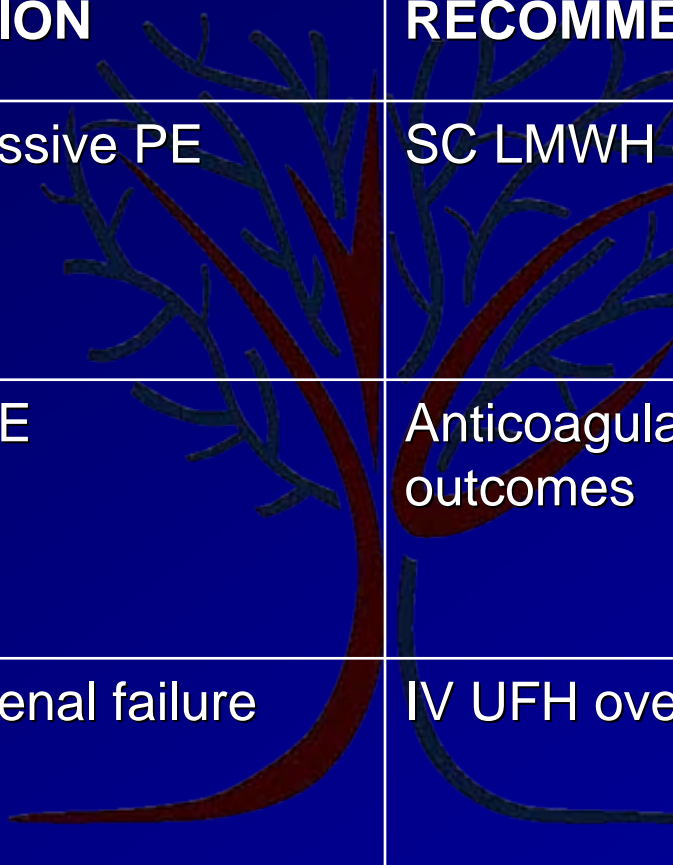


Long-term Therapy for DVT

PATIENT CHARACTERISTICS	RECOMMENDED TREATMENT
First DVT episode and any of the following: documented antithrombin deficiency, deficiency of protein C or protein S, factor V Leiden, prothrombin 20210 gene mutation, homocystinemia, factor VIII levels > 90 th percentile of normal	VKA therapy for 6 to 12 months Suggest continuing treatment indefinitely
2 or more episodes of documented DVT	Suggest continuing treatment indefinitely



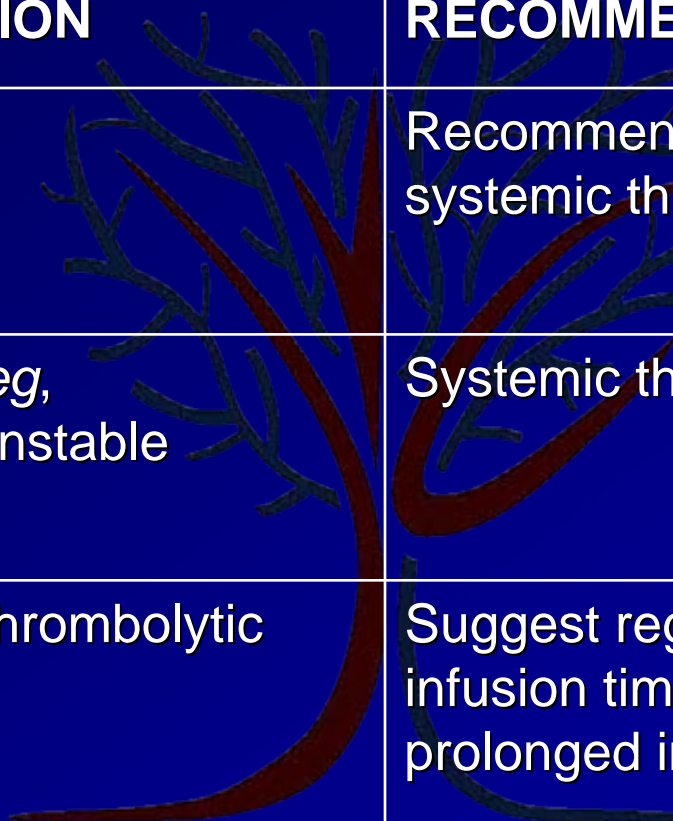
Initial Therapy for PE: LMWH Or UFH Therapy



CLINICAL SITUATION	RECOMMENDATION
Confirmed, non-massive PE	SC LMWH or IV UFH
High suspicion of PE	Anticoagulants, while awaiting test outcomes
Coexisting severe renal failure	IV UFH over LMWH



Initial Therapy for PE: Thrombolytic Agents

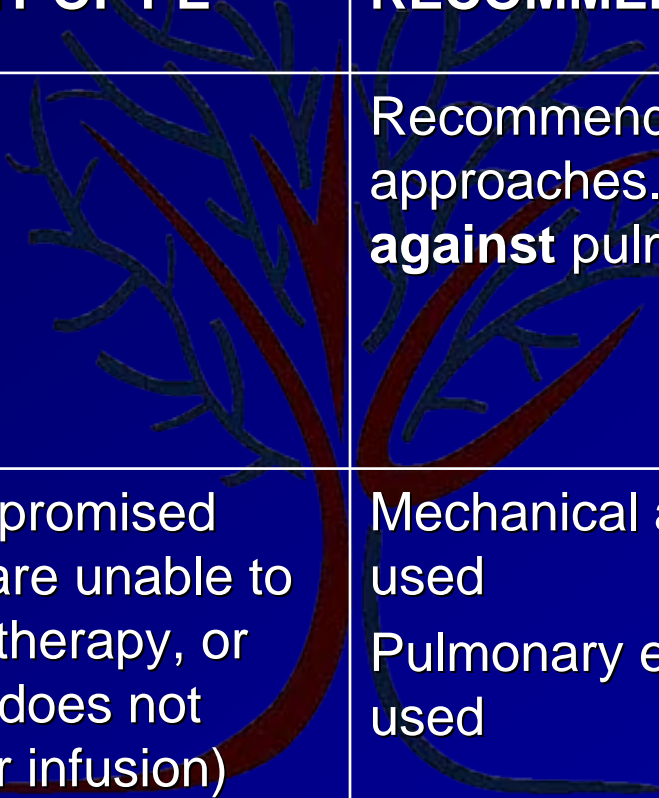


CLINICAL SITUATION	RECOMMENDATION
Most patients	Recommend clinicians not use systemic thrombolytic therapy
Selected patients, eg, hemodynamically unstable patients	Systemic thrombolytic therapy
Patients receiving thrombolytic therapy	Suggest regimens with a short infusion time over those with a prolonged infusion time



Initial Therapy for PE: Additional Recommendations

INITIAL TREATMENT OF PE	RECOMMENDATION
Most patients	Recommend against mechanical approaches. Recommend against pulmonary embolectomy.
Selected, highly compromised patients (those who are unable to receive thrombolytic therapy, or whose critical status does not allow enough time for infusion)	Mechanical approaches may be used Pulmonary embolectomy may be used



Initial Therapy for PE: Additional Recommendations

INITIAL TREATMENT OF PE	RECOMMENDATION
Patients with a contraindication for, or complication of, anticoagulant treatment; or patients with recurrent thromboembolism, despite adequate anticoagulation therapy	Suggest clinicians place an IVC filter



Long-Term Therapy for PE: VKA Therapy

PATIENT CHARACTERISTICS	RECOMMENDATION
First episode of PE, secondary to a transient (reversible) risk factor	VKA therapy for ≥ 3 months
First episode of idiopathic PE	VKA therapy for ≥ 6 to 12 months Consider giving anticoagulants indefinitely
Concomitant cancer	Most patients: LMWH for 3 to 6 months; then anticoagulants indefinitely, or until the cancer is resolved



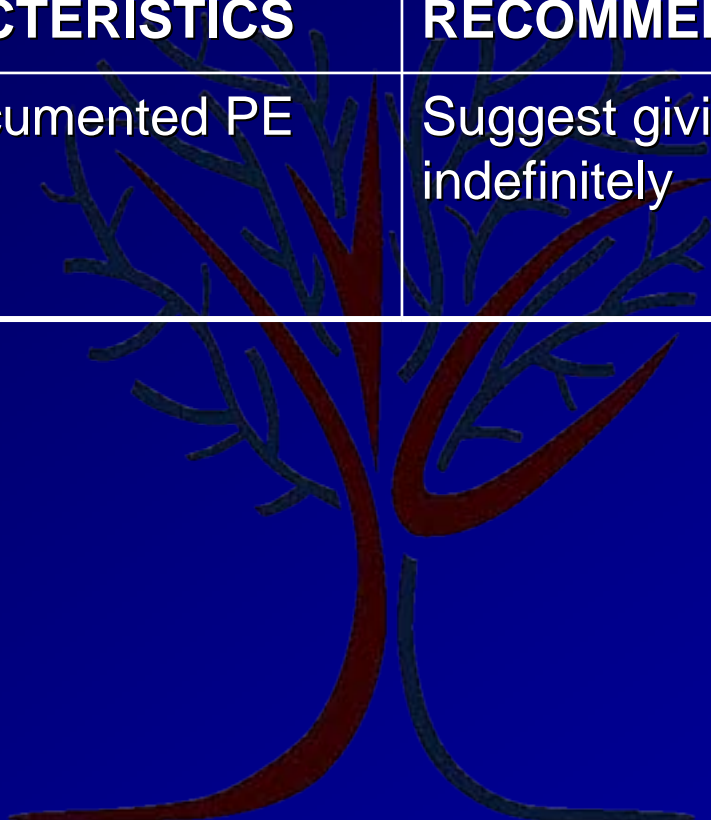
Long-Term Therapy for PE: VKA Therapy

PATIENT CHARACTERISTICS	RECOMMENDATION
First episode of PE, and either documented APLAs or ≥ 2 thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations)	Treat for 12 months; Suggest giving anticoagulants indefinitely
First episode of PE, and any of the following: documented antithrombin deficiency, protein C or protein S deficiency, factor V Leiden, prothrombin 20210 gene mutation, homocystinemia, high factor VIII levels ($> 90^{\text{th}}$ percentile of normal)	Treat for 6 to 12 months Suggest giving anticoagulants indefinitely



Long-Term Therapy for PE: VKA Therapy

PATIENT CHARACTERISTICS	RECOMMENDATION
≥ 2 episodes of documented PE	Suggest giving anticoagulants indefinitely



Postthrombotic Syndrome aka “Chronic Thrombophlebitis”

- 5% of population
 - 6-7 million people have venous stasis changes
 - 400,000-500,000 have ulcers
- Causes more socioeconomic morbidity than PE
- After DVT, develops in 30%-80%
 - Pain
 - Edema
 - Hyperpigmentation
 - ulceration



Postthrombotic Syndrome

- Caused by ambulatory venous hypertension
 - Valvular reflux
 - Persistent venous obstruction
- Not inevitable after DVT
 - 31% of involved extremities show no reflux on duplex 1 year after event
- Can we predict who is susceptible
 - Recurrent thrombotic events
 - Long recanalization time
 - Proximal DVT



Postthrombotic Syndrome

- Cumulative incidence continues to rise for 20 years after initial episode.



Postthrombotic Syndrome: Prevention

- 30-40 mm HG Compression Stockings
 - Reduce cumulative incidence of PTS at 2 years
 - You would decrease your risk by 70%
- Recommendation is for immediate initiation after diagnosis and continuation of therapy for 2 years
 - 30-40 mm Hg



Postthrombotic Syndrome without Ulcers

■ Severe edema

- Stockings did not show significant benefit
- Intermittent pneumatic compression at 40 mm Hg was beneficial
 - Improved symptoms
 - No ulcers
 - *study not powered for ulcers



■ Mild edema

- Elastic compression stockings



Postthrombotic Syndrome with Ulcers

■ Venous Ulcers

- Primary venous insufficiency vs. Postthrombotic
- Postthrombotic limbs
 - Higher venous pressures
 - More likely to have ulceration
- Treatment
 - IPC devices if resistant to wound care and compression
 - Surgical treatment of superficial venous reflux
 - Hyperbaric oxygen did not show benefit

■ *only one study



Postthrombotic Syndrome with Ulcers

■ Treatment Venous Ulcers

■ Pentoxifylline 400mg po tid

- Cochrane review of 8 RCT's
- In addition to wound care and compression +/- IPC



Postthrombotic Syndrome with Ulcers

■ Treatment Venous Ulcers

■ Rutosides

- Micronized Purified Flavanoid Fraction (Daflon 500mg)
- Sulodexide (Sulonex)
 - Reduce capillary permeability
 - Reduce inflammation
 - Improve lymphatic function
 - Improve symptoms
- Recommend addition to local wound care and compression
- RCT's showed 32% RR reduction for persistent ulcers



