Management of VTE

By DR

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Objectives

- Recognize **subgroups** of VTE
- Review **medications** for VTE anticoagulation
- Learn guidelines for **duration** of therapy
- **Understand differences** in therapy based on type of VTE

Subgroups of VTE

- Cancer-associated vs No cancer
- Provoked vs Unprovoked
- Proximal vs Distal DVT
- Upper extremity vs Lower extremity DVT

Location of VTE

- **Lower extremity DVT**
  - Proximal – Popliteal or more proximal veins
  - Distal – Calf veins
- **Upper extremity DVT**
  - Proximal – Axillary or more proximal veins
  - Catheter-associated

Antithrombotic Therapy for VTE: CHEST Guidelines 2016

BACKGROUND: We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

METHODS: We generate strong (Grade 1) and weak (Grade 2) recommendations based on high- (Grade A), moderate- (Grade B), and low- (Grade C) quality evidence

proximal DVT or (PE)

- 1. we **recommend** long-term

(*3 months*) **anticoagulant therapy** over no such therapy (Grade 1B).

VTE and No cancer

- *2., as long-term (first 3 months) anticoagulant therapy, we **suggest** (NOACS)dabigatran, rivaroxaban, apixaban, or edoxaban **over** vitamin K antagonist (VKA) therapy (all Grade 2B).
- For patients who are **not treated with OR CI to** dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over low-molecular weight heparin (LMWH) (Grade 2C).

Remarks: **Initial parenteral anticoagulation** is given before dabigatran and edoxaban, (Start with parenteral anticoagulation x5 days)

- is not given before rivaroxaban and apixaban,
- and is overlapped with VKA therapy. (And INR >2 for 24 hours)

Contraindications to NOACs

- Extreme BMI (>40)
- Cr Cl <30
- Significant increased risk of bleeding

Which is the best NOAC

based on indirect comparisons, the risk of bleeding may be lower with **apixaban** than with the other NOACs and

despite the lack of specific reversal agents for the NOACs, **the risk that a major bleed will be fatal** appears to be no higher for the NOACs than for VKA therapy.

Based on less bleeding with NOACs and greater convenience for patients and healthcare providers, we now suggest that a NOAC is used in preference to VKA for the initial and long-term treatment of VTE **in patients without cancer**

- Extended treatment with dabigatran, rivaroxaban, and apixaban markedly reduces recurrent VTE without being associated with much bleeding
- **dabigatran** is as effective and as safe as VKA **for extended treatment** of VTE and provide moderate quality evidence that each of the NOACs are effective at preventing recurrent VTE without being associated with a high risk of bleeding

NOACs

Drug	Brand name	Target	Peak (h)	Half-life (h)	Bio	Renal excr. (%)	Drug interactions
Dabigatran	Pradaxa®	Factor IIa	1.5	14 - 17	8%	> 80%	P-glycoprotein
Rivaroxaban	Xarelto®	Factor Xa	2 - 3	7 - 11	80%	33%	CYP3A4 P-glycoprotein
Apixaban	Eliquis ®	Factor Xa	3	8 – 14	66%	25%	CYP3A4 P-glycoprotein
Edoxaban	Lixiana ®	Factor Xa	4	8 - 11	45%	35%	CYP3A4 P-glycoprotein

OHRI IRSO

RIVAROXABAN (XARELTO; BAYER)
Usual dose: 20mg od with food. **Bioavailability:** 66% (without food), almost 100% (with food). **Peak plasma level:** 2–4 hrs. **Half-life:** 5–9 hrs (young), 11–13 hrs (elderly). **Renal excretion:** 35%. **Liver metabolism:** yes.
Interactions: Use with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics or HIV protease inhibitors, is not recommended. Co-administration with dronedarone and strong CYP3A4 inducers should be avoided.

DABIGATRAN ETEXILATE
(PRADAXA; BOEHRINGER INGELHEIM)
Usual dose: 150mg bid. **Bioavailability:** 3–7%. **Peak plasma level:** 2hrs. **Half-life:** 12–17hrs. **Renal excretion:** 80%. **Liver metabolism:** no.
Interactions: Use with strong P-gp inhibitors ketoconazole, cyclosporine, itraconazole and dronedarone is contraindicated. Use with P-gp inhibitor verapamil requires dose reduction. Use with P-gp inducers should be avoided.

APIXABAN
(ELIQUIS; BRISTOL-MYERS SQUIBB-PFIZER)
Usual dose: 5mg bid. **Bioavailability:** 50%. **Peak plasma level:** 1–4 hrs. **Half-life:** 12 hrs. **Renal excretion:** 27%. **Liver metabolism:** yes.
Interactions: Use with strong inhibitors of CYP3A4 or P-glycoprotein (P-gp) is not recommended. Use with strong inducers of CYP3A4 and P-gp requires caution.

EDOXABAN (LIXIANA; DAIICHI SANKYO UK)
Usual dose: 60 mg od. **Bioavailability:** 62%. **Peak plasma level:** 1–2 hrs. **Half-life:** 10–14 hrs. **Renal excretion:** 50%. **Liver metabolism:** minimal.
Interactions: Use with the P-gp inhibitors ciclosporin, dronedarone, erythromycin or ketoconazole requires dose reduction to 30mg once daily. Use with caution concomitantly with P-gp inducers (e.g. rifampicin).

- The order of our presentation of the NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) is based on the chronology of publication of the phase 3 trials in VTE treatment and should not be interpreted as the guideline panel's order of preference for the use of these agents.
- In the absence of direct comparisons between NOACs, and no convincing indirect evidence that one NOAC is superior to another, we do **not have a preference for one NOAC over another NOAC**

WHY NOT IN CANCER

NOAC INTERACTIONS WITH ANTICANCER THERAPIES BASED ON KNOWN METABOLIC PATHWAYS

Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein CYP3A4
Increases NOAC plasma levels†	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
Reduces NOAC plasma levels‡	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

Novel oral anticoagulants may not be suitable for use in some cancer patients because they share metabolic pathways. Further research is needed to find out more about the impact of the interaction

† Inhibitors of pgp transport and CYP34A pathway. ‡ Inducers – lower NOAC levels

("**cancer**-associated thrombosis")

- *3. , as long-term (first 3 months)anticoagulant therapy, we **suggest LMWH** over
- VKA therapy (Grade 2C),
- dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C),or edoxaban (Grade 2C).

factors that influence choice of therapy

We suggested VKA therapy over LMWH in **patients without cancer** for the following reasons:

- injections are burdensome; LMWH is expensive;
- there are low rates of recurrence with VKA in patients with VTE without cancer; and VKA may be as effective as LMWH in patients without cancer.

We suggested LMWH over VKA in **patients with cancer** for the following reasons:

there is moderate-quality evidence that LMWH was more effective than VKA in patients with cancer; there is a substantial rate of recurrent VTE in patients with VTE and cancer who are treated with VKA;

it is often harder to keep patients with cancer who are on VKA in the therapeutic range;

LMWH is reliable in patients who have difficulty with oral therapy (eg, vomiting); and LMWH is easier to withhold or adjust than VKA if invasive interventions are required or thrombocytopenia develops.

TABLE 6] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

INR = International Normalized Ratio; NOAC = non-vitamin K oral coagulant. See Table 1 legend for expansion of other abbreviations.

extended therapy FOR VTE

- *4., we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).
- Remarks: It may be appropriate for the choice of anticoagulant to change in response to changes in the patient's circumstances or preferences during long-term or extended phases of treatment.

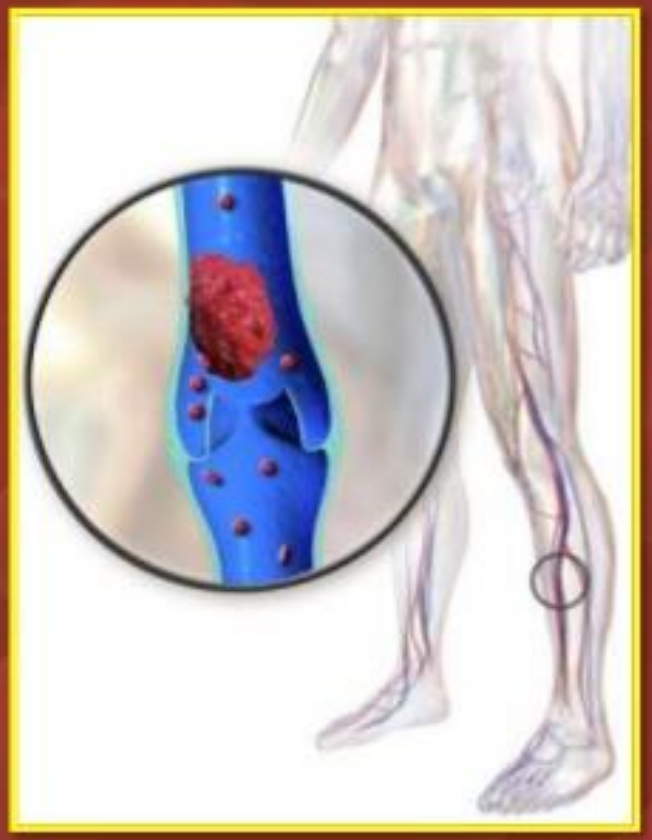
DOSE CHANGE

- We have revised the wording of this recommendation to make it clearer that we neither encourage nor discourage use of the same anticoagulant for initial and extended therapy.
- Although we anticipate that the anticoagulant that was used for initial treatment will often also be used for the extended therapy, We also **note that whereas apixaban 5 mg twice daily is used for long-term treatment, apixaban 2.5 mg twice daily is used for extended therapy**

Hypercoaguliablity:

Cancer- chemotherapy.
Estrogen / OCP
Nephrotic syndrome.
Sepsis
HRT
Antiphospholibid
Hyperhomocystinuria.
Thrombophilia

- Ant thrombin deficiency.
- Protein C deficiency.
- Protein S Deficiency.
- Factor V Leiden.




Who's at risk for VTE?
Not moving for a long time
Staying in the hospital or having surgery
VTE risk factors
Some genetic abnormalities
Having cancer
Smoking
Taking birth control pills
Having a baby
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Provoking **Transient** Risk Factors for VTE

- Surgery
- Estrogen therapy
- Pregnancy
- Leg injury
- Flight >8h

RECURRENCE RISK

- (1) VTE provoked by **surgery** (a major transient risk factor; 3% recurrence at **5 years**);
- (2) VTE provoked by a **nonsurgical transient risk** factor (eg, estrogen therapy, pregnancy, leg injury, flight of >8 h; 15% recurrence at 5 years);
- (3) **unprovoked** (also termed "idiopathic") VTE; not meeting criteria for provoked by a transient risk factor or by cancer (30% recurrence at 5 years); and
- (4) VTE associated with cancer (also termed "**cancer associated thrombosis**"; **15% annualized risk of recurrence**; recurrence at 5 years not estimated because of high mortality from cancer)

AFTER WHAT

Recurrence risk was further stratified by estimating the risk of recurrence after:

- (1) **an isolated distal DVT** was half that after a **proximal DVT or PE** and
- (2) a **second un provoked proximal** DVT or PE was 50% higher (1.5-fold) than after **a first unprovoked event**.

For the decision about whether to stop treatment at 3 months or to treat indefinitely ("extended treatment"), we categorized a patient's risk of bleeding on anticoagulant therapy as

- Low (no bleeding risk factors; 0.8% annualized risk of major bleeding),
- moderate (one bleeding risk factor; 1.6% annualized risk of major bleeding), or
- high (two or more bleeding risk factors; 6.5% annualized risk of major bleeding)

TABLE 11] Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories[a]

Risk Factors[b]	Categorization of Risk of Bleeding[d]		
	Estimated Absolute Risk of Major Bleeding		
	Low Risk[e] (0 Risk Factors)	Moderate Risk[e] (1 Risk Factor)	High Risk[e] (≥2 Risk Factors)
Age >65 y[184-193]			
Age >75 y[184-188,190,192,194-202]			
Previous bleeding[185,191-193,198,201-204]			
Cancer[187,191,195,198,205]			
Metastatic cancer[181,204]			
Renal failure[185,191-193,196,199,201,206]			
Liver failure[186,189,195,196]			
Thrombocytopenia[195,204]			
Previous stroke[185,192,195,207]			
Diabetes[185,186,196,200,202]			
Anaemia[185,189,195,198,202]			
Antiplatelet therapy[186,195,196,202,208]			
Poor anticoagulant control[189,196,203]			
Comorbidity and reduced functional capacity[191,196,204]			
Recent surgery[189,209,c]			
Frequent falls[195]			
Alcohol abuse[191,192,195,202]			
Nonsteroidal anti-inflammatory drug[210]			
Anticoagulation 0-3 mo[f]			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6[g]	3.2	12.8[h]
Anticoagulation after first 3 mo[f]			
Baseline risk (%/y)	0.3[i]	0.6	≥2.5
Increased risk (%/y)	0.5	1.0	≥4.0
Total risk (%/y)	0.8[j]	1.6[j]	≥6.5

AT9 = 9th Edition of the Antithrombotic Guideline.

Warfarin:

- Vitamin K antagonist . Avoid rich food of Vit K.
- Avoid drugs that interact with warfarin.
- Avoid the IM injection.
- Tell your surgeon about your warfarin thereby.

Table 2: Common Medications with Possible Interactions with Warfarin

Medication	Effect on international normalized ratio	Proposed Mechanism
acetaminophen	increase	inhibition of metabolism
allopurinol	increase	inhibition of metabolism
aprepitant/fosaprepitant	decrease	induction of CYP2C9 metabolism
azathioprine	decrease	decrease in absorption, increase in metabolism
azithromycin	increase	inhibition of CYP3A4
carbamazepine	decrease	induction of metabolism
celecoxib	increase	inhibition of CYP2C9
ciprofloxacin	increase	inhibition of CYP3A4 and CYP1A2
clarithromycin	increase	inhibition of CYP3A4
corticosteroids	increase/decrease	unknown
cyclosporine	decrease	unknown
direct thrombin inhibitors (argatroban, lepirudin)	additive anti-coagulant activity	direct pharmacologic action
erythromycin	increase	inhibition of CYP3A4
fluconazole	increase	inhibition of CYP3A4 and CYP2C9
fluoroquinolones	increase	inhibition of CYP1A2
heparin/low–molecular-weight heparins	additive anti-coagulant activity	direct pharmacologic action
itraconazole	increase	inhibition of CYP3A4
metronidazole	increase	inhibition of CYP2C9
NSAIDs	no effect	increased bleeding risk
omeprazole	increase	inhibition of CYP2C19
phenytoin/ Fosphenytoin	increase/decrease	changes in metabolism of CYP2C9, CYP2C19 and CYP3A4
rifampin	decrease	induction of metabolism
SSRIs	increase	changes in metabolism
sulfamethoxazole	increase	inhibition of CYP2C9

compare different time-limited durations of therapy

- A **VKA** targeted to an (INR) of about 2.5 was the anticoagulant in all studies .
- We, therefore, assumed that VKA therapy was the anticoagulant when we were making our AT9 recommendations, including for the comparison of extended therapy with stopping treatment at 3 months.

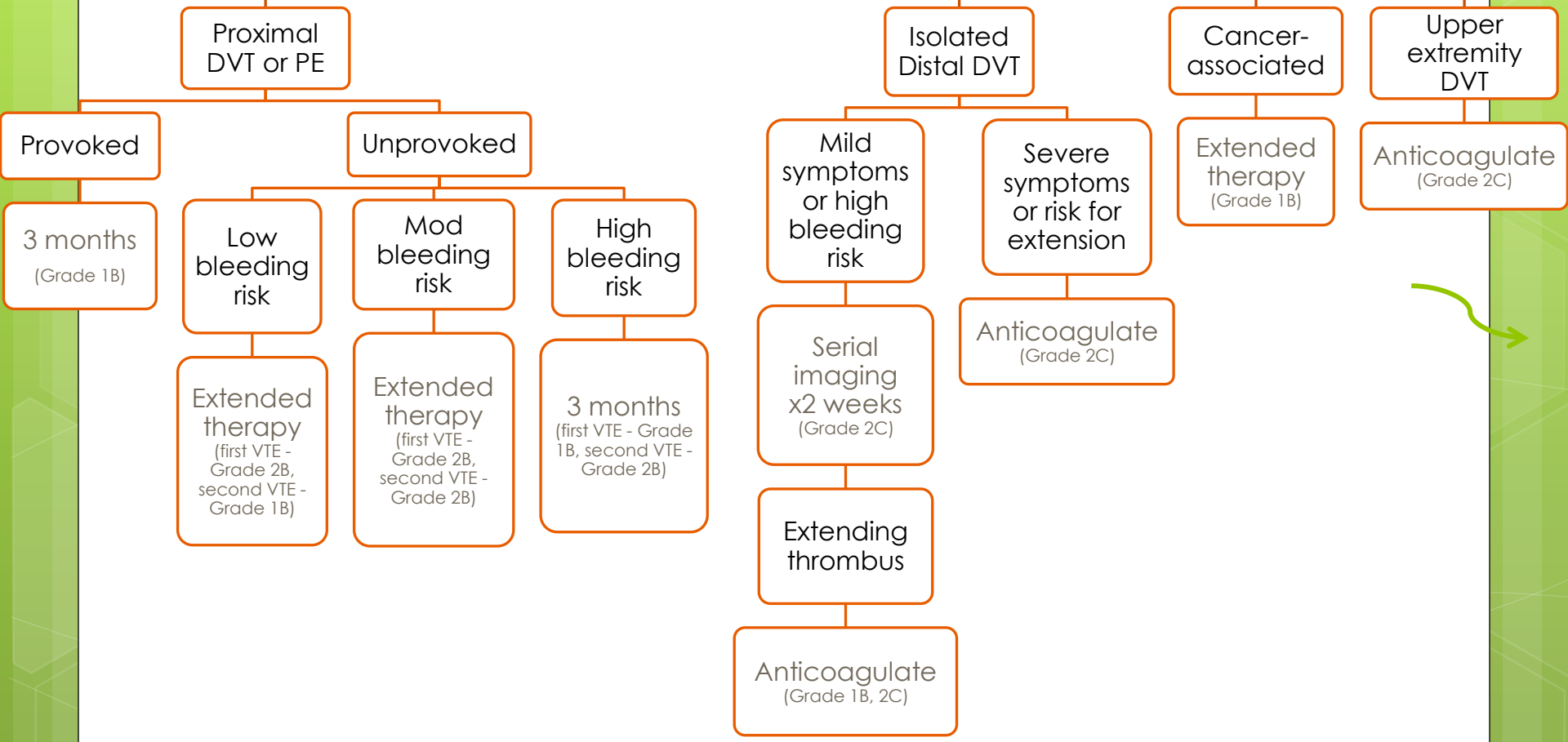
AT9 recommendations

on how long VTE should be treated were based on comparisons of four durations of treatment:

- (1) 4 or 6 weeks
- (2) 3 months;
- (3) longer than 3 months but still a time-limited course of therapy (usually 6 or 12 months); or
- (4) extended (also termed “indefinite”; no scheduled stopping date) therapy.1

These four options were assessed in four subgroups of VTE patients with different estimated risks of recurrence after stopping anticoagulant therapy

Duration of Therapy



Duration of Anticoagulant Therapy

5. In patients with a proximal DVT of the leg or PE **provoked by surgery**, we recommend treatment with anticoagulation for 3 months over

- (i) treatment of a shorter period (Grade 1B),
- (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months)(Grade 1B), or
- (iii) extended therapy (no scheduled stop date) (Grade 1B).

proximal DVT of the leg or PE

- 6. provoked by a **nonsurgical transient risk factor**, we **recommend** treatment with anticoagulation for 3 months over
- (i) treatment of a shorter period (Grade 1B) and
- (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).
- We **suggest** treatment with anticoagulation for 3 months over extended therapy if there is a **low or moderate bleeding risk** (Grade 2B), and
- **recommend** treatment for 3 months ONLY over extended therapy if there is a **high risk of bleeding** (Grade 1B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

isolated distal DVT

- 7. **provoked** by surgery or by a nonsurgical transient risk factor, we **suggest** treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C),
- we **recommend** treatment with anticoagulation for **3 months** over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B), and
- we **recommend** treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Duration of treatment of patients with **isolated distal** DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however,it is anticipated that *not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants*.

unprovoked DVT of the leg

- 8. (**isolated distal or proximal**) or **PE**, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

Remarks: After 3 months of treatment, patients with unprovoked DVT of the leg or PE **should be evaluated for the risk-benefit** ratio of extended therapy.

first VTE that is an unprovoked

- 9. **proxima**l DVT of the leg or PE and who have a
- (i) low or moderate bleeding risk ,we suggest **extended** anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and
- (ii) high bleeding risk, we recommend **3 months** of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Patient **sex** and **D-dimer level measured a month after stopping anticoagulant therapy** may influence the decision to stop or extend anticoagulant therapy

In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be **reassessed at periodic intervals (eg, annually).**

- **Men** have about a 75% higher (1.75-fold) risk of recurrence compared with women, whereas patients with a **positive D-dimer** result have about double the risk of recurrence compared with those with a negative D-dimer, and the predictive value of these two factors appears to be additive.
- The risk of recurrence in women with a negative post treatment D-dimer appears to be similar to the risk that we have estimated for patients with a proximal DVT or PE that was provoked by a minor transient risk factor (approximately 15% recurrence at 5 years)
- consequently, the argument for extended anticoagulation in these women is not strong, suggesting that D-dimer testing **will often influence a woman's decision**.
- The risk of recurrence in men with a negative D-dimer is not much less than the overall risk of recurrence that we have estimated for patients with an unprovoked proximal DVT or PE (approximately 25% compared with approximately 30% recurrence at 5 years);
- consequently, the argument for extended anticoagulation in these men is still substantial, suggesting that D-dimer testing **will often not influence a male's decision**.
- **Because there is still uncertainty about how to use D-dimer testing and a patient's sex to make decisions about extended therapy in patients with a first unprovoked VTE, we have not made recommendations based on these factors.**

D- dimer:

Degenration product of cross-linked fibrin.

- Sensitivity 97%.
- Specificity 35%.
- It remains high for 7 days in DVT.
- Used to rule out DVT.
- False +ve D-dimer include surgery, recent MI, acute infection, DIC, pregnancy or recent delivery, Metastatic cancer.

second unprovoked VTE

10. who have a

- (i) low bleeding risk , we **recommend** extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B);
- (ii) moderate bleeding risk , we **suggest** extended anticoagulant therapy over 3months of therapy (Grade 2B); or
- (iii) high bleeding risk , we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, **annually**).

("cancer-associated thrombosis")

- 11. who
- (i) do **not** have a high bleeding risk, we **recommend** extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or
- (ii) have a high bleeding risk, we **suggest** extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

Compression Ultrasonography (DACUS) study

- In patients with a first proximal DVT or PE and active cancer who had residual DVT on US imaging after completing 6 months of LMWH therapy, the Cancer-Duration of Anticoagulation based on the study which randomized patients to another 6 months of LMWH or to stop therapy and followed patients for 12 months after they stopped LMWH.
- The additional 6 months of LMWH reduced recurrent VTE but, **once anticoagulation was stopped, the risk of recurrent VTE was the same** in those who had been treated for 6 or for 12 months.
- In the same study, all patients without residual DVT after 6 months of LMWH stopped therapy and had a low risk of recurrence during the next year (three episodes in 91 patients).
- This study's findings have not changed our recommendations for treatment of VTE in patients with cancer.

Whether and How to Anticoagulate

Isolated Distal DVT

13.

- (i) **without severe symptoms or risk factors for extension** we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C)
- (ii) with severe symptoms or risk factors for extension ,we suggest anticoagulation over serial imaging of the deep veins (Grade 2C).

Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging.

Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

In AT9

- , we judged that there was high-quality evidence that anticoagulant therapy was effective for the treatment of **proximal** DVT and PE,
- but **uncertainty** that the benefits of anticoagulation outweigh its risks in patients with isolated distal DVT because of their lower risk of progressive or recurrent VTE.

- AT9 discouraged **routine whole-leg US examinations** (ie, including the distal veins) in patients with suspected DVT, thereby reducing how often isolated distal DVT is diagnosed.

The rationale for not routinely examining the distal veins in patients who have had proximal DVT excluded is that

- : (1) other assessment may already indicate that isolated distal DVT is either unlikely to be present or unlikely to cause complications if it is present (eg, low clinical probability of DVT, D-dimer is negative);
- (2) if these conditions are not met, a repeat US examination of the proximal veins can be done after a week to detect possible DVT extension and the need for treatment; and
- (3) **false-positive findings** for DVT occur more often with US examinations of the distal compared with the proximal veins

If the calf veins are imaged (usually with US) and isolated distal DVT is diagnosed, there are **two management options**:

- (1) treat patients with anticoagulant therapy or
- (2) do not treat patients with anticoagulant therapy unless extension of their DVT is detected on a follow-up US examination (eg, after 1 and2 weeks, or sooner if there is concern;

there is no widely accepted protocol for surveillance US testing). Because about **15% of untreated isolated distal DVT are expected to subsequently extend** into the popliteal vein and may cause PE, **it is not acceptable to neither anticoagulate nor do surveillance to detect thrombus extension.**

risk factors for extension

of distal DVT that would favor anticoagulation over surveillance:

(1) D-dimer is positive (particularly when markedly so without an alternative reason);

(2) thrombosis is extensive (eg, >5 cm in length, involves multiple veins, >7 mm in maximum diameter);

(3) thrombosis is close to the proximal veins;

(4) there is no reversible provoking factor for DVT;

(5) active cancer;

(6) History of VTE; and

(7) inpatient status

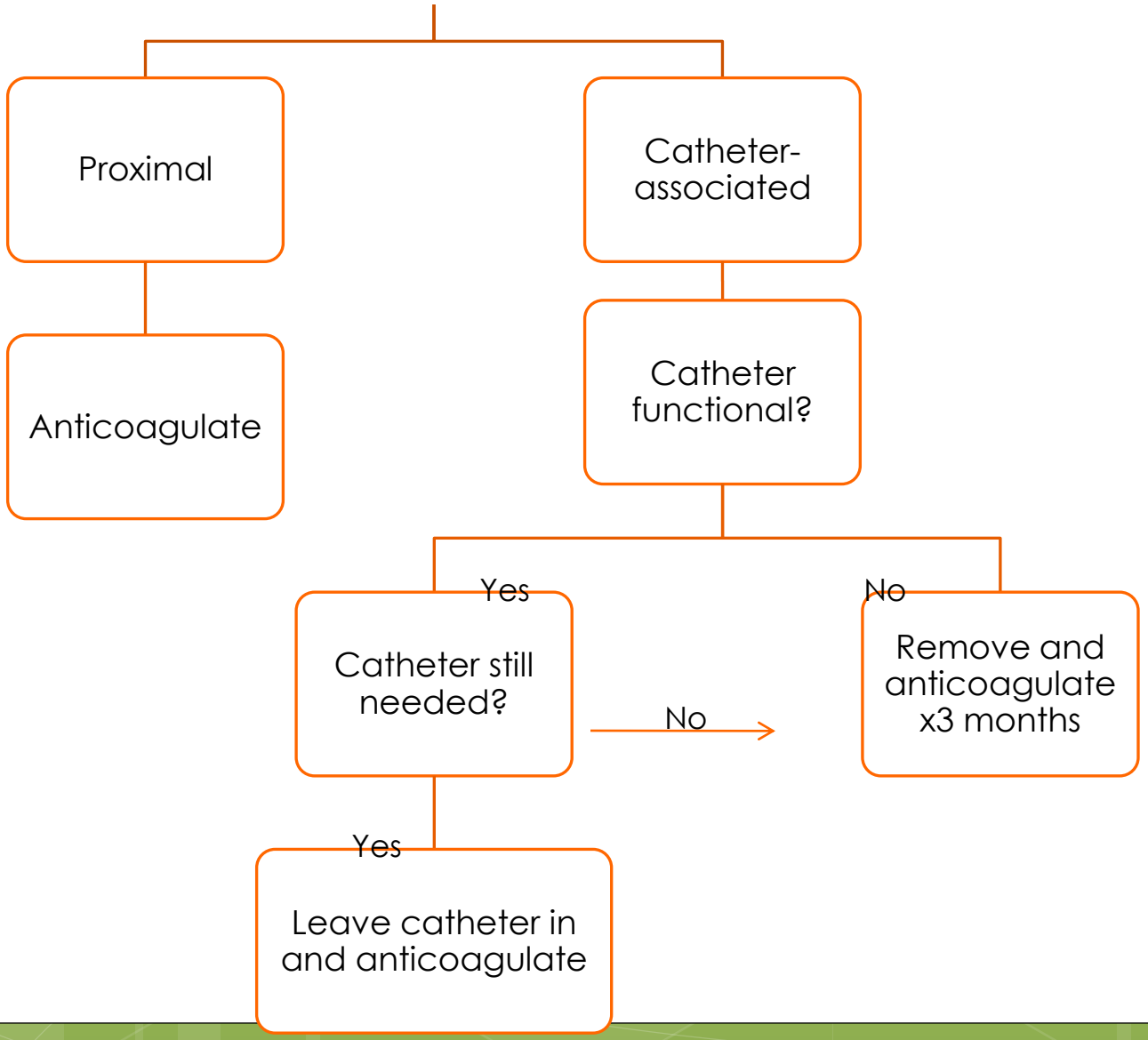
- 15. In patients with acute isolated distal DVT of the leg who are **managed with serial imaging**, we
- (i) **recommend** no anticoagulation if the thrombus does not extend (Grade 1B),
- (ii) suggest anticoagulation if the thrombus extends but *remains confined* to the distal veins (Grade 2C), and
- (iii) **recommend** anticoagulation if the thrombus extends *into the proximal veins* (Grade 1B).

muscular veins of the calf

- We consider thrombosis that is confined to the muscular veins of the calf (ie,, soleus, gastrocnemius) to have a lower risk of extension than thrombosis that involves the axial (ie, true deep; peroneal, tibial) veins.
- **Severe symptoms** favor anticoagulation, **a high risk for bleeding** favors surveillance, and the decision to use anticoagulation or surveillance is expected to be sensitive to patient preferences.
- We anticipate that isolated distal DVT that are detected using a selective approach to whole-leg US will often satisfy criteria for initial anticoagulation, whereas distal DVT detected by routine whole-leg US often will not.
- The evidence supporting these recommendations remains low quality because it is not based on direct comparisons of the two management strategies, and ability to predict extension of distal DVT is limited.

- 14. In patients with **acute isolated distal DVT** of the leg who are managed with anticoagulation, we recommend using the same anticoagulation as for patients with **acute proximal** DVT (Grade 1B).

Special Considerations for Upper Extremity DVT



Management of Recurrent VTE on Anticoagulant Therapy

- *29. In patients who have recurrent VTE on **VKA therapy** (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest **switching** to treatment with LMWH at least temporarily (minimum1 month) (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments:

- (1) reevaluation of whether there truly was a recurrent VTE;
- (2) evaluation of compliance with anticoagulant therapy; and
- (3) consideration of an underlying malignancy.

- *30. In patients who have recurrent VTE on **long term LMWH** (and are believed to be compliant), we suggest **increasing the dose** of LMWH by about 25-33% (Grade 2C).

- There are no randomized trials or prospective cohort studies that have evaluated management of patients with recurrent VTE on anticoagulant therapy
- Risk factors for recurrent VTE while on anticoagulant therapy can be divided into two broad categories:
- (1) treatment factors and
- (2) the patient's intrinsic risk of recurrence.

How a new event should be treated will depend on the reason(s) for recurrence.

Treatment Factors:

- The risk of recurrent VTE decreases rapidly after starting anticoagulant therapy, with a **much higher risk during the first week** (or month) compared with the second week (or month).
- A recurrence soon after starting therapy can generally be managed by a time-limited (eg, 1 month) period of more aggressive anticoagulant intensity (eg, switching from an oral agent back to LMWH, an increase in LMWH dose).
- Other treatment factors that are associated with recurrent VTE and will suggest specific approaches to management include:
- (1) was LMWH being used; (2) was the patient adherent; (3) was VKA subtherapeutic; (4) was anticoagulant therapy prescribed correctly;
- (5) was the patient taking an NOAC and a drug that reduced anticoagulant effect; and (6) had anticoagulant dose been reduced (drugs other than VKA)?

- There is moderate-quality evidence that LMWH is more effective than VKA therapy in patients with **VTE and cancer.**
- A switch to full-dose LMWH, therefore, is often made if there has been an unexplained recurrent VTE on VKA therapy or an NOAC.
- If the recurrence happened on LMWH, the dose of LMWH can be increased. If the dose of LMWH was previously reduced (eg, by 25% after 1 month of treatment), it is usually increased to the previous level.
- If the patient was receiving full-dose LMWH, the dose may be increased by about 25%.
- **In practice**, the increase in dose is often influenced by the LMWH prefilled syringe dose options that are available.
- Once-daily LMWH may also be switched to a twice daily regimen, particularly if two injections are required to deliver the increase in LMWH dose.
- Treatment adherence, including compliance, can be difficult to assess; for example, symptoms of a recurrent DVT may encourage medication adherence and a return of coagulation results to the "therapeutic range."

Patient Factors

- : The most important is **active cancer**, with an unexplained recurrence often pointing to yet-to-be-diagnosed disease.
- **Antiphospholipid syndrome** is also associated with recurrent VTE, either because of associated hypercoagulability or because a lupus anticoagulant has led to underdosing of VKA because of spurious increases in INR results.
- Anticoagulated patients may be taking **medications** that increase the risk of thrombosis such as estrogens or cancer chemotherapy, in which case these treatments may be withdrawn.

INR

around 2.5

- DVT
- PE
- AF

around 3.5

- recurrent DVT
- Anti phospholipids.
- Prosthetic valves.
- Coronary artery graft thrombosis.

cancer patients with recurrent VTE

- A retrospective observational study found an acceptable risk of recurrence (8.6%) and major bleeding (1.4%) during 3 months of follow-up in 70 pts while on anticoagulant therapy who either switched from VKA therapy to LMWH (23 patients) or had their LMWH dose increased by about 25% (47 patients).
- If there is no reversible reason for recurrent VTE while on anticoagulant therapy, and anticoagulant intensity cannot be increased because of risk of bleeding, a **vena caval filter** can be inserted to prevent PE.However, it is not known if insertion of a filter in these circumstances is worthwhile, and the AT10 panel consider this an option of last resort

Role of IVC Filter in Addition to Anticoagulation for Acute DVT or PE

- 17. In patients with acute DVT or PE who are **treated with anticoagulants**, we recommend against the use of an IVC filter (Grade 1B).

- WITHOUT anticoagulation, the risk that PE will develop in patients with venous thromboembolism is high, and **PE may be fatal in as many as 25% of patients**.

Indications of IVC filter

- **The primary indication** for the insertion of an IVC filter is the occurrence of a complication of or contraindication for anticoagulation therapy.
- **Less frequent indications** for the insertion of an IVC filter are recurrent thromboembolism despite adequate anticoagulation therapy and chronic recurrent pulmonary embolism with pulmonary hypertension.
- Finally, IVC filters have been used for pulmonary embolism **prophylaxis** in patients with proximal DVT who are at high risk for bleeding and selected trauma patients (pelvic fracture) who are at high risk for VTE and cannot be managed with effective prophylaxis.
- Anticoagulation should be continued whenever possible to prevent further thrombosis.

BOX 53-1

Evidence-Based Guidelines, Relative Expanded Indications for, and Contraindications to Vena Cava Filter Placement

EVIDENCE-BASED GUIDELINES

- Documented VTE with contraindication to anticoagulation
- Documented VTE with complications of anticoagulation
- Recurrent PE despite therapeutic anticoagulation
- Documented VTE with inability to achieve therapeutic anticoagulation

RELATIVE EXPANDED INDICATIONS

- Poor compliance with anticoagulation
- Free-floating iliocaval thrombus
- Renal cell carcinoma with renal vein extension
- Venous thrombolysis/thromboembolectomy
- Documented VTE and limited cardiopulmonary reserve
- Documented VTE with high risk for anticoagulation complications
- Recurrent PE complicated by pulmonary hypertension
- Documented VTE—cancer patient
- Documented VTE—burn patient
- Documented VTE—pregnancy
- VTE prophylaxis—high-risk surgical patient
- VTE prophylaxis—trauma patient
- VTE prophylaxis—high-risk medical condition

CONTRAINDICATIONS

- Chronically occluded vena cava
- Vena cava anomalies
- Inability to access the vena cava
- Vena cava compression
- No location in the vena cava available for placement

PE, Pulmonary embolism; *VTE*, venous thromboembolism.

PREPIC trial

- Our recommendation in AT9 was primarily based on findings of the Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (**PREPIC**) randomized trial, which showed that placement of a permanent IVC filter increased DVT, decreased PE, and did not influence VTE (DVT and PE combined) or mortality.
- Since then, several registries have suggested that IVC filters can reduce early mortality in patients with acute VTE, although this evidence has been questioned.

PREPIC 2 randomized trial

- The recently published PREPIC 2 randomized trial found that placement of an IVC filter for 3 months did not reduce recurrent PE, including fatal PE, in **anticoagulated** patients with PE and DVT who had additional risk factors for recurrent VTE
- This new evidence is consistent with our recommendations in AT9. However, because it is uncertain if there is benefit to placement of an IVC filter in anticoagulated **patients with severe PE** (eg, with hypotension), and this is done by some experts, our recommendation against insertion of an IVC filter in patients with acute PE who are anticoagulated may not apply to this select subgroup of patients.
- Although the PREPIC 2 study has improved the quality of evidence for this recommendation, overall quality is still moderate because of imprecision
- The AT10 panel decided against combining the results of the PREPIC and PREPIC 2 studies because of differences in the type of filter used, the duration of filter placement, and differences in the length of follow-up

- No randomized trials or prospective cohort studies have evaluated IVC filters as sole therapy for acute PE

TYPES OF IVC FILTERS

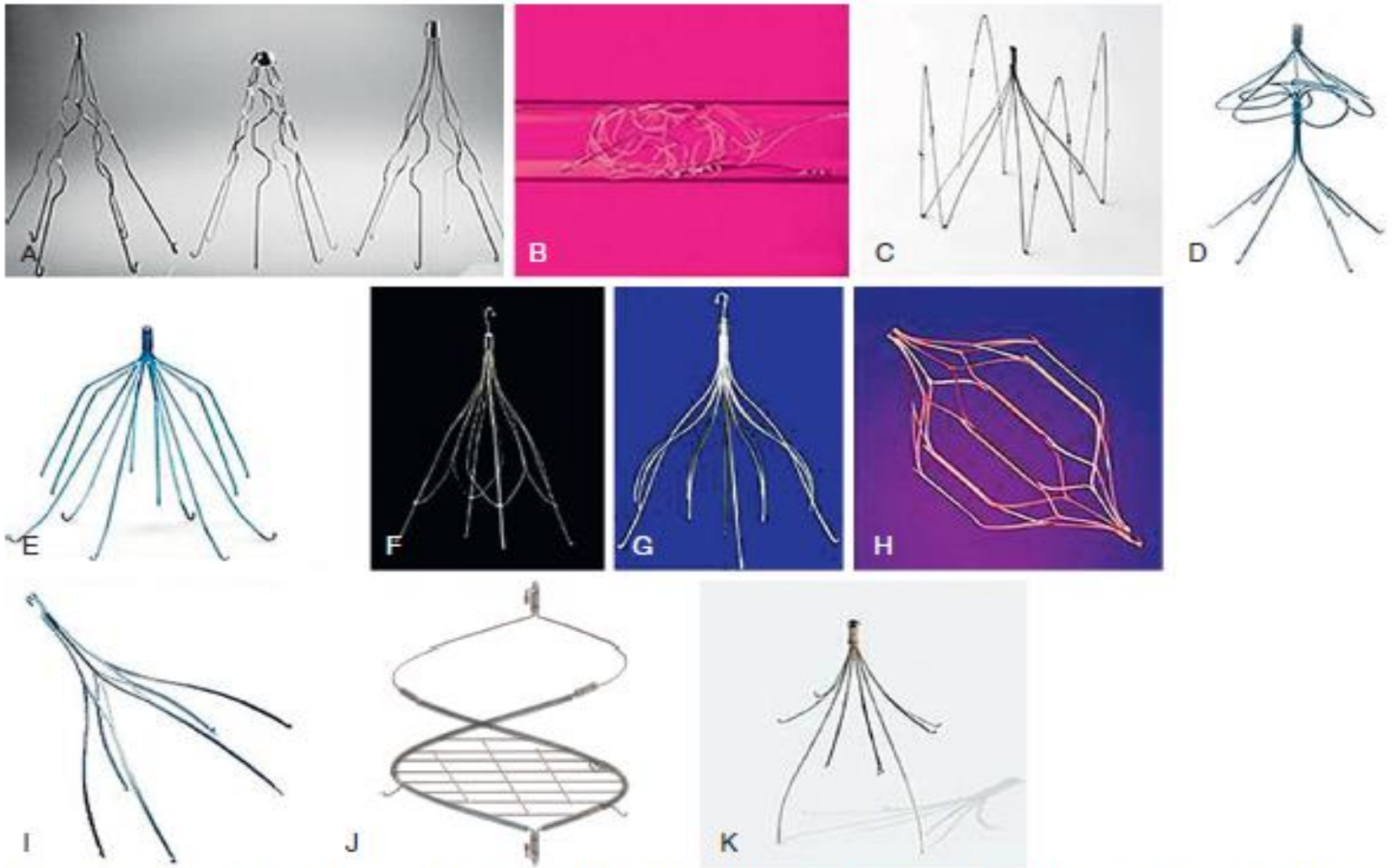


Figure 53-2 Vena cava filter designs currently approved by the U.S. Food and Drug Administration. **A,** *From left to right,* Boston Scientific titanium Greenfield filter, original stainless steel Greenfield filter, and low-profile stainless steel Greenfield filter; **B,** Cook Medical Gianturco-Roehm Bird's Nest filter; **C,** Vena Tech LP filter; **D,** Bard Peripheral Vascular/Simon Nitinol filter; **E,** Bard Peripheral Vascular Recovery G-2 filter; **F,** Cook Medical Günther Tulip filter; **G,** Cook Celect filter; **H,** Cordis Corporation OPTEASE filter; **I,** Argon Medical Devices Option filter; **J,** Crux VCF (Volcano Corporation, San Diego, Calif); **K,** ALN International Inc Optional filter. Not pictured, Bard Peripheral Vascular Eclipse filter and Bard Peripheral Vascular Meridian filter.

Vena cava filter design categories include the following:

- • ***Permanent filter***: Placed with the intention of providing permanent, lifelong filtration, a permanent filter has design characteristics that maximize secure fixation.
- • ***Temporary filter***: Not currently available in the United States, the temporary filter is not designed for permanent placement and does not have any means of fixation to the vena cava wall. Rather, such a filter is attached to a wire or catheter that traverses the venous system and either protrudes from the skin or is buried in adjacent subcutaneous tissue. Removal is required before the filter or tether becomes incorporated
- • ***Convertible filter***: Functioning initially as a permanent filter with elements allowing attachment to the vena cava wall, a convertible filter can be altered structurally after implantation to non filtration state with removal of the filtration portion through a separate percutaneous procedure.
- • ***Optional/retrievable filter***: Similar to a conventional permanent filter, the optional or retrievable filter has the added feature of removal capability. A retrievable filter adheres to the wall of the vena cava with hooks, barbs or radial force (or any combination of the three) but can be retrieved by image-guided catheter techniques within a device-specific time interval.

retrievable filter

- designs need to have sufficient incorporation to prevent migration but not so much that retrieval cannot be accomplished. Altering the filter hook contact point to allow retrievability may have the disadvantage of a greater tendency for filter leg penetration or filter migration.
- This change has also resulted in different filter hook lengths and angle configurations.
- Although some filters, such as the Greenfield filter, incorporate a recurved configuration to create a contact angle of 80 degrees, allowing better hook incorporation without full penetration into the vena cava, other filters use a j-hook configuration to prevent excessive incorporation and facilitate retrievability

Retrievable filters

- Retrievable filters were developed to take advantage of short term PE prevention benefits, without the long-term disadvantages of increasing DVTs

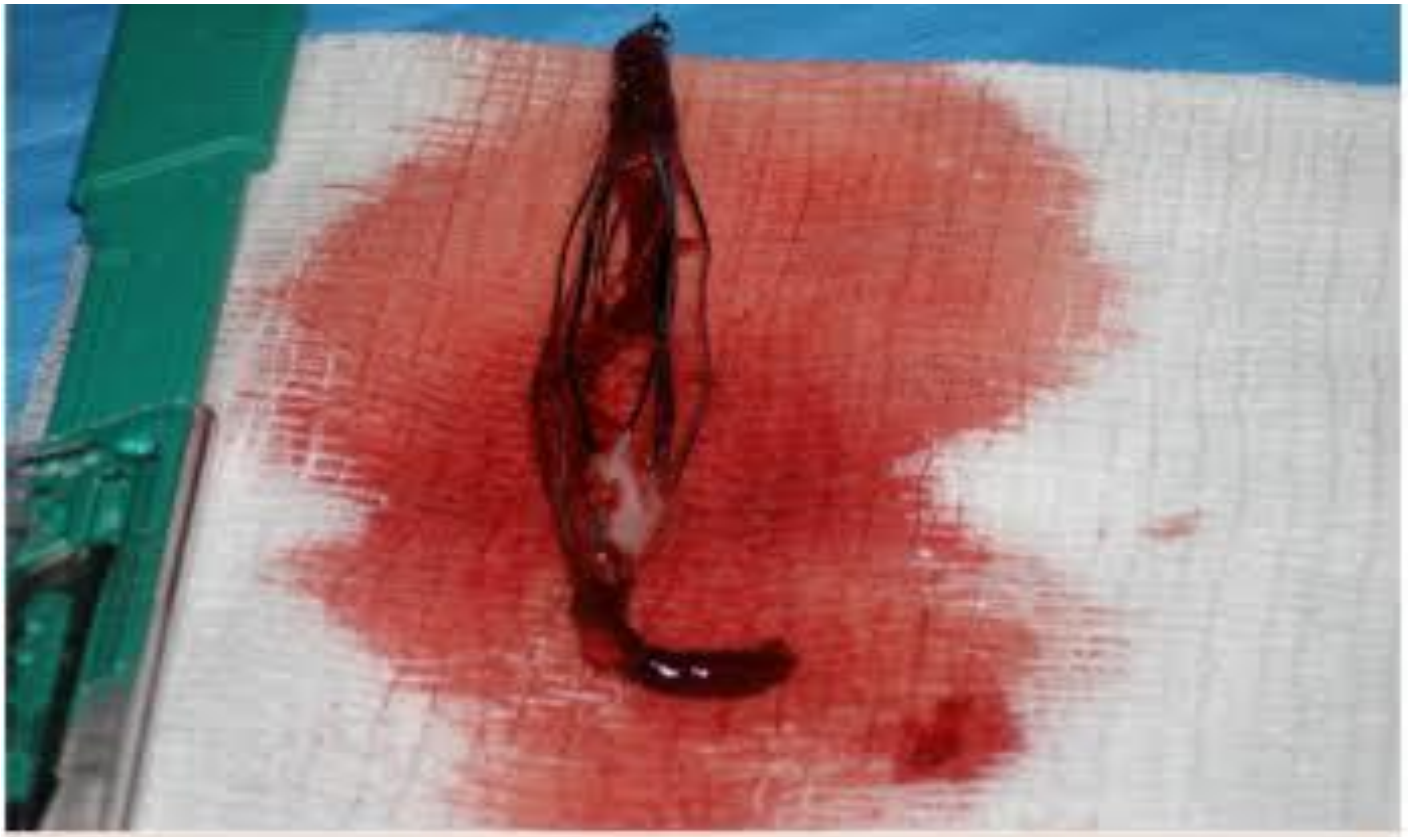


Figure 4. Removal of an Optease inferior vena cava filter (Cordis Corporation) 3 months after implantation. Note avulsed tissue and adherent thrombus.

Most "retrievable" IVC filters are not removed, in real-world practice

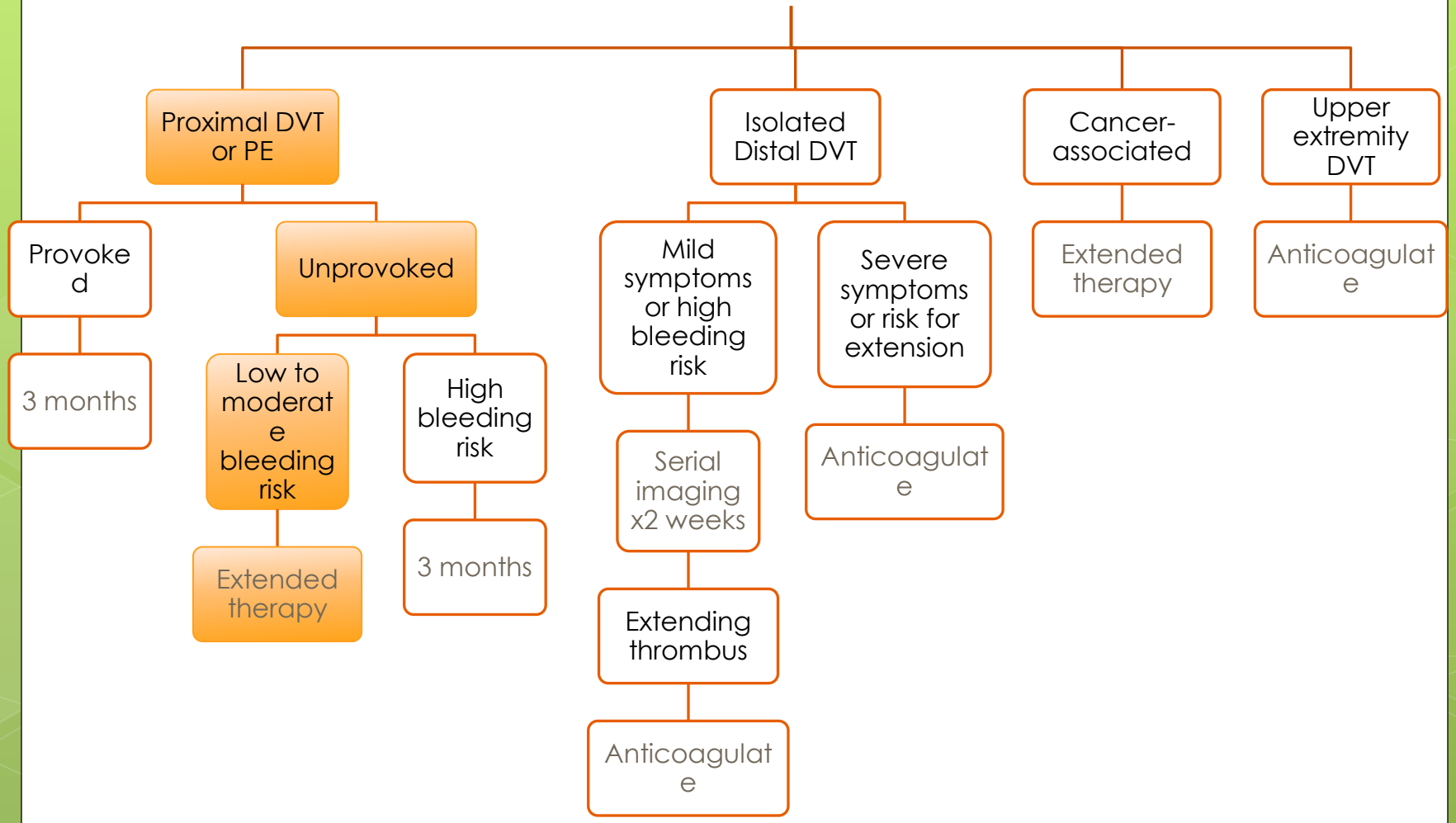
- Retrieval rate 34% (range 12-45%)
- Average time to retrieval 72 days
- Mean follow up after filter placement 10 months (range2-25 months)
- Overall retrieval failure rate 5.5%, increased with time - Most common causes were tilting (43%), adherence to the IVC wall (39%), and large clot burden (18%)
- Most common reasons for not removing filter were loss to follow up and continued risk

Angel et al., J Vasc Interv Radiol 2011; 22: 1522-1530

Comparison of Different **Time-Limited Durations** of Anticoagulation

- Since AT9: Two additional studies have compared **two time-limited durations of anticoagulant therapy.**
- In patients with a **first unprovoked PE** who had completed 6 months of VKA therapy (target INR 2.5), the Extended Duration of Oral Anticoagulant Therapy After a First Episode of Idiopathic Pulmonary Embolism: a Randomized Controlled Trial **(PADIS) study** randomized patients to another 18 months of treatment or to placebo, and then followed both groups of patients for an additional 24 months after study drug was stopped
- The study's findings were consistent with our recommendations in AT9; the **additional 18 months of VKA was very effective** at preventing recurrent VTE but, once anticoagulation was stopped, the risk of recurrent VTE was the same in those who had been treated for 6 or for 24 months.
- This new information has not increased the quality of evidence for comparison of a longer vs a shorter, time-limited course of anticoagulation **in patients without cancer**

Duration of Therapy



Evaluations of Extended Anticoagulant Therapy Since AT9:

- When AT9 was written, extended treatment of VTE with VKA therapy had been evaluated in six studies (mostly patients **with unprovoked proximal DVT or PE** or a **second episode of VTE**), and with **an NOAC** (rivaroxaban vs placebo) in one study of heterogeneous patients.21
- Since AT9, no studies have compared extended VKA therapy with stopping anticoagulants, although the large reduction in recurrent VTE with 18 additional months of VKA therapy compared with placebo (ie, before study drug was stopped)
- in the **PADIS study** supports AT9 estimates for the efficacy of extended VKA therapy.
- Since AT9, two additional studies have compared **extended NOAC therapy** (dabigatran,47 apixaban48) with stopping treatment (ie, placebo). These two studies, and the previous study that evaluated extended treatment with rivaroxaban, found that extended therapy with these three NOAC regimens reduced recurrent VTE by at least 80% and was associated with a modest risk of bleeding
- These three studies, however, enrolled heterogeneous populations of patients (ie, not confined to unprovoked VTE) and only followed patients for 6 to 12 months, which limits the implications of their findings in relationship to extended therapy.

based on VKA therapy

- When considering the risks and benefits of extended anticoagulation in this update, the AT10 panel decided to use the same estimates for the reduction in recurrent VTE and the increase in bleeding with anticoagulation that we used in AT9, and that were based on VKA therapy.

Our reasoning was:

- (1) VKA is still widely used for extended treatment of VTE;
- (2) we felt that there was not enough evidence of differences in efficacy and bleeding during extended therapy to justify separate recommendations for NOACs, either as a group or as individual agents;
- (3) our recommendations about whether or not to use extended therapy were not sensitive to assuming that there was a one-third reduction in bleeding with extended therapy compared with the estimated risk of bleeding with extended therapy

CDT for Acute DVT of the Leg

- 16. we suggest anticoagulant therapy alone over CDT (Grade 2C).
- Remarks: Patients who are most likely to benefit from CDT ,who attach a high value to prevention of PTS, and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.

Catheter Directed Thrombolysis (CDT)

- **Indications:**

  Acute ilio-femoral DVT

  Multi level DVT

  Massive DVT (Phlegmasia)

  < 10 days old

- **Contraindications:**

Absolute	Strong Relative	Other Relative
Active bleeding / DIC Recent CVA / TIA Neurosurgery or Intracranial Trauma (<3 months)	Recent Major Surgery Major Trauma(<10 days) Eye surgery (<3 months) Major GIT bleed (<3 mo) Uncontrolled HPT(>180) Recent delivery (<10 d) ICSOL or seizure disorder Recent CPR (< 10 d)	Renal failure Severe hepatic dysfunction Bacterial endocarditis Diabetic haemorrhagic Retinopathy Pregnancy or lactation

mechanism

- The delivery of the plasminogen activator within the thrombus is more effective and potentially safer than systemic infusion of plasminogen activators.
- Additionally, intrathrombus delivery protects plasminogen activators from circulating plasminogen activator inhibitor, and more importantly, protects the active enzyme plasmin from neutralization by circulating antiplasmin.
- This neutralization of circulating plasminogen is so effective that the half-life of plasmin in the systemic circulation is only a fraction of a second.
- Most bleeding complications are localized to the venous access site.
- Symptomatic PE during infusion is uncommon, and fatal PE is a rarity.
- A cohort-controlled QoL study was performed to determine whether lytic therapy altered QoL in patients with iliofemoral DVT in the National Venous Registry.
- Results demonstrated that CDT was associated with better QoL than anticoagulation alone.

[CAVENT] Study)

- Larger randomized trial (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis **[CAVENT] Study)** assessing short-term (eg, venous patency and bleeding) but not long-term (eg, PTS) outcomes.
- reported that CDT reduced PTS, did not alter quality of life, and appears to be cost-effective
- A retrospective analysis found that CDT (3649 patients) was associated with an increase in transfusion (twofold), intracranial bleeding (threefold), PE (1.5-fold), and vena caval filter insertion (twofold); **long-term outcomes and PTS were not reported.**

recently

- The recently published CaVenT trial reported the longterm outcome after additional CDT versus anticoagulation alone for acute iliofemoral DVT.
- These investigators randomized 209 patients. Their primary endpoint was iliofemoral patency at 6 months and PTS at 2 years.
- CDT was performed with the **UniFuse catheter** (AngioDynamics, Latham, NY).
- Alteplase was infused at a dose of 0.01 mg/kg/hr for a maximum of 96 hours. The alteplase was prepared by mixing 20 mg in 500 mL of 0.9% sodium chloride. This resulted in a 70-kg man being infused with 0.7 mg of (rt-PA) in 17.5 mL of infusate. This appears to be an unusually small volume of infusate, which might potentially be a disadvantage in patients.
- The mean duration of thrombolysis was 24 days; 43% of patients had complete thrombolysis, 37% had partial, and thrombolysis was unsuccessful in 10%. Patients receiving CDT had a mean clot resolution of 82%.
- Patients treated with additional CDT had significantly improved iliofemoral venous patency at 6 months ($P = .012$) and less PTS at 2 years ($P = .047$).


Uni·Fuse™
INFUSION CATHETER

- The authors reported that **lower thrombus scores** at completion of CDT were associated with increased patency ($P < .04$), and that **patency** of the iliofemoral venous system correlated with a reduction in PTS ($P < .001$).
- There was an absolute risk reduction in PTS of 14.4% in patients who received CDT.
- Major bleeding complications occurred in 3.3% of patients who underwent CDT.
- Only one inferior vena cava filter was used in this group, and no symptomatic pulmonary embolism (PE) was observed

ATTRACT trial

- A much larger study, the ATTRACT trial, sponsored by the National Institutes of Health, is prospectively randomizing patients with symptomatic proximal DVT.36
- The target sample size is 692 patients. Patients with iliofemoral and femoropopliteal DVT will be stratified at entry into the study to catheter-based techniques of thrombolysis versus anticoagulation alone.
- The primary endpoint is PTS at 24 months.
- The ATTRACT trial **will** also evaluate relative benefits of pharmacomechanical techniques versus the CDT drip technique and **will** include a careful cost analysis.

Pharmacomechanical Thrombolysis

- Although good results can be achieved with CDT, **treatment times** are often unacceptably long, and therefore, bleeding risk and cost associated with therapy are unacceptably high
- treatment time for CDT averaged 71 hours. This duration of acute care is logistically difficult, if not impossible, for many practitioners and many medical centers.

The associated cost is high because all patients receiving lytic therapy are generally monitored in ICUs.

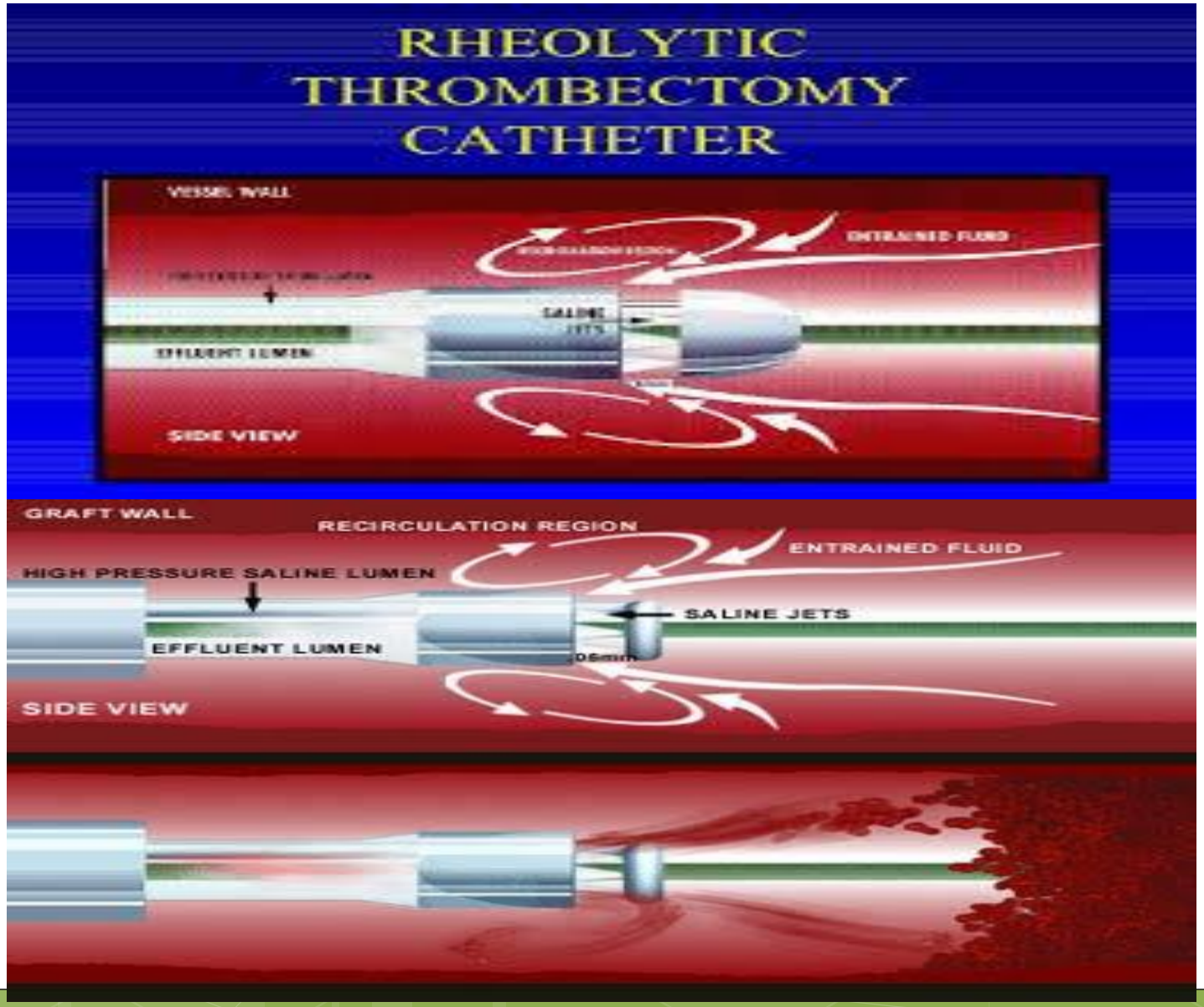
Endovascular Mechanical Thrombectomy

- . Mechanical techniques alone or in combination with thrombolysis have been developed to more rapidly clear the venous system
- multiple devices, including the **Amplatz** (ev3, Inc., Plymouth, Minn), **AngioJet** (Possis Medical, Minneapolis, Minn), **Trerotola** (Arrow International,Reading, Penn), and **Oasis** (Boston Scientific/Medi-tech, Natick, Mass) catheters.
- 26%of the thrombus was removed by mechanical thrombectomy alone, whereas adding a plasminogen activator solution to the mechanical technique (pharmacomechanical) removed 82% of the thrombus.


ARROW-Trerotola™ PTD®
Percutaneous Thrombolytic Device
Most proven mechanical thrombectomy technology
available for dialysis access.

rheolytic thrombectomy catheter.

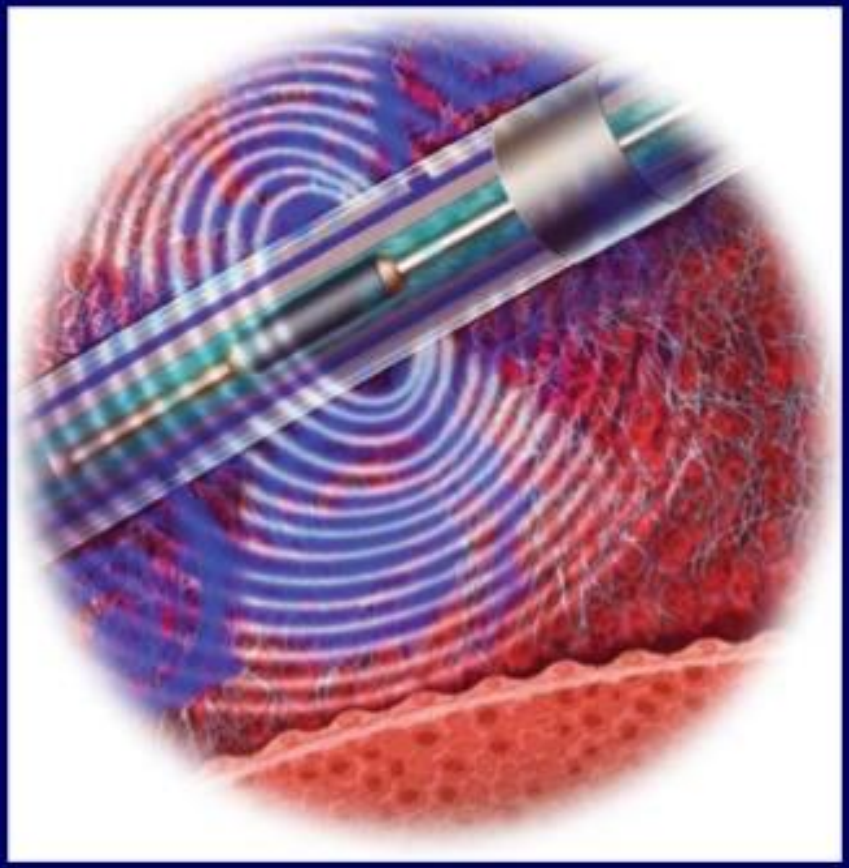
- Lin et al32 reported their 8-year experience with pharmacomechanical thrombolysis via a rheolytic thrombectomy catheter.
- Of their 98 patients, 46 received CDT alone and 52 underwent pharmacomechanical thrombolysis. Pharmacomechanical thrombolysis with the **AngioJet catheter** was associated with significantly fewer phlebograms, shorter ICU stays, shorter hospital stays, and fewer blood transfusions.
- Bleeding complications were not different between the two groups.


RHEOLYTIC
THROMBECTOMY
CATHETER
VESSEL WALL
ENTRAINED FLUID
SALINE
JETS
EFFLUENT LUMEN
SIDE VIEW
GRAFT WALL
RECIRCULATION REGION
ENTRAINED FLUID
HIGH PRESSURE SALINE LUMEN
SALINE JETS
EFFLUENT LUMEN
SIDE VIEW

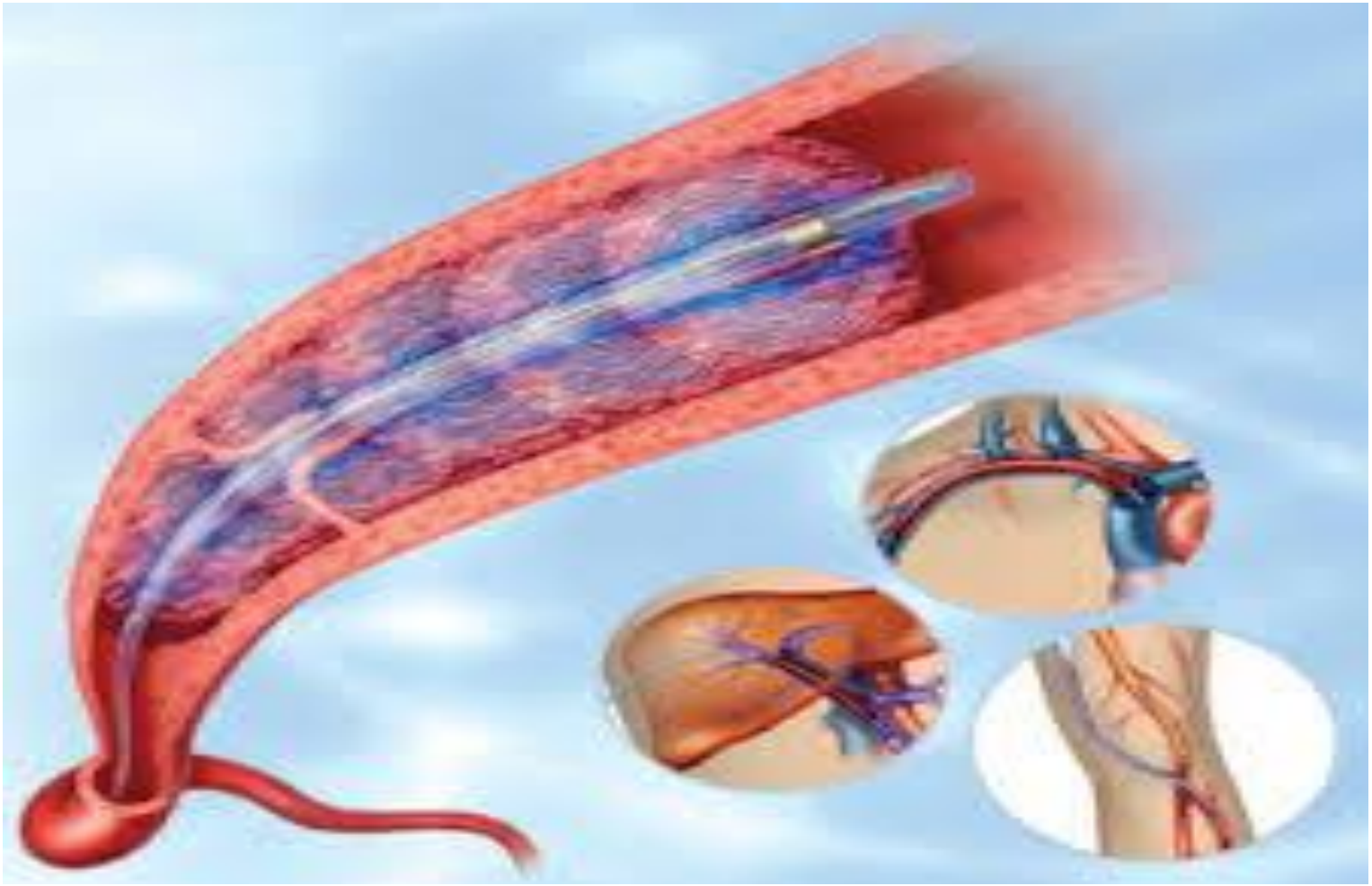
Ultrasound Accelerated Thrombolysis

- 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

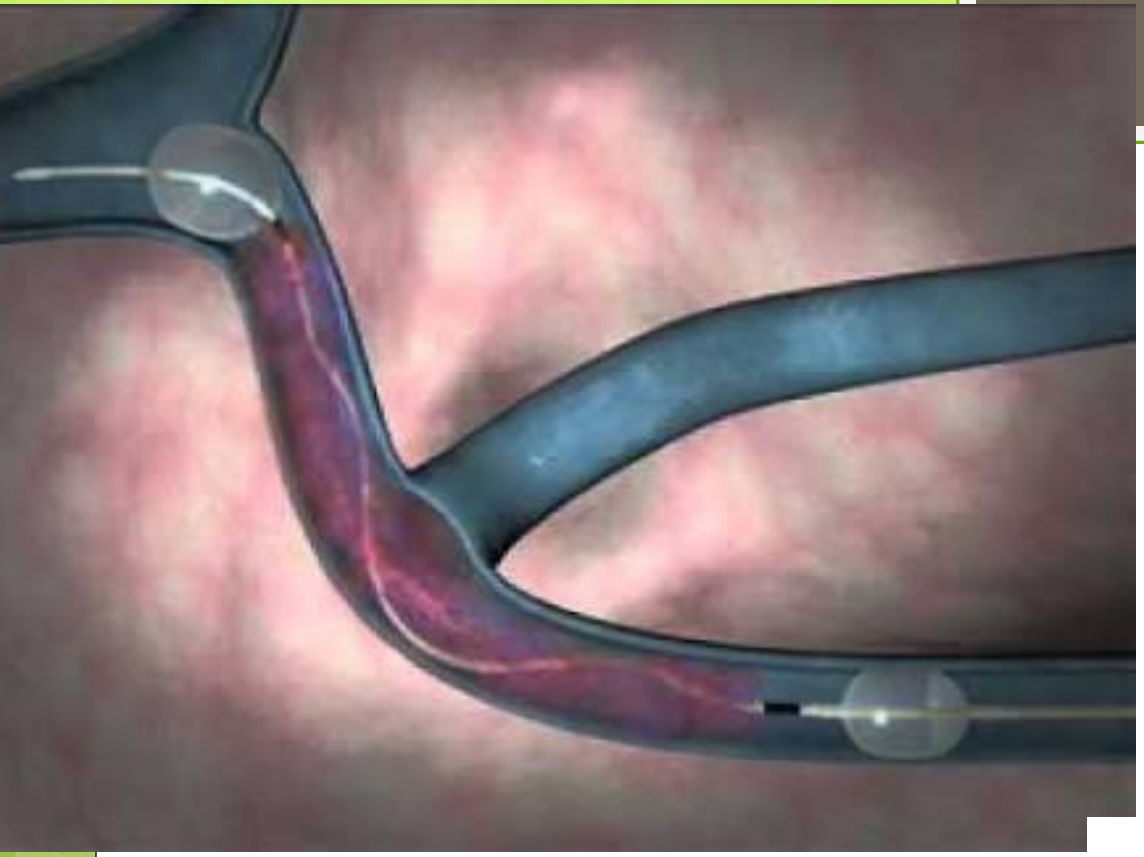


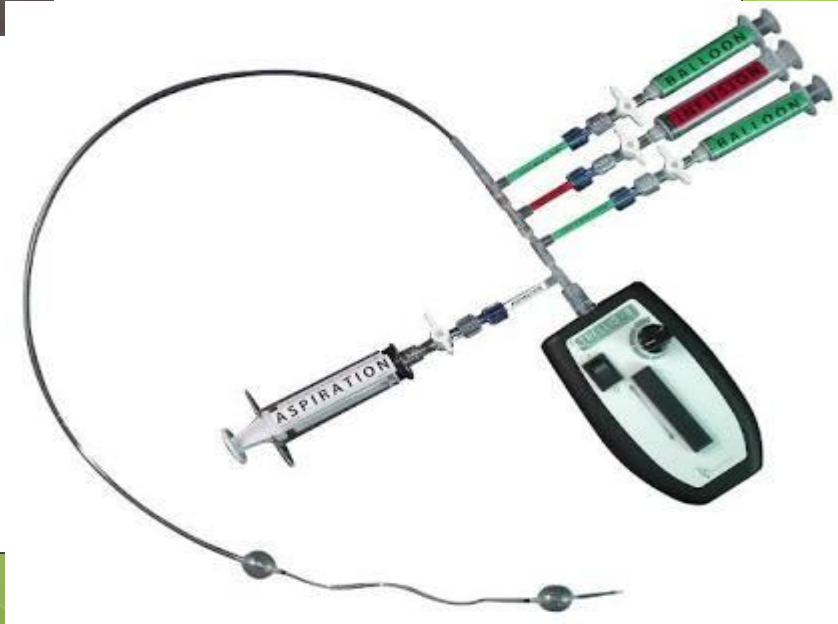
Example and principle of the EKOS ultrasound facilitated thrombolysis (Courtesy of EKOS Corp., Bothell, WA.)



Isolated Segmental Pharmacomechanical Thrombolysis

- An interesting new technique (ISPMT), which is achieved by using the **Trellis catheter** (Covidien, Mansfield, Mass). This double-balloon catheter is inserted into the thrombosed venous segment with the proximal balloon positioned at the upper edge (cephalic end) of the thrombus.
- When the balloons are inflated, plasminogen activator is infused into the thrombosed segment isolated by the balloons.
- The intervening catheter assumes a spiral configuration and **spins at 1500 rpm for 15 to 20 minutes**. The liquefied and fragmented thrombus is aspirated and treatment success evaluated by repeat segmental phlebography.
- If successful, the catheter is repositioned and additional thrombosed segments are treated; if residual thrombus persists, repeat treatment or **other appropriate intervention** (rheolytic thrombectomy, ultrasound-accelerated thrombolysis, balloon angioplasty, stenting) is performed
- A larger percentage of the thrombus was removed with ISPMT than with CDT. **Complete lysis (≥90%)** was achieved in 11% of the limbs of CDT patients as opposed to 28% of the limbs treated by ISPMT ($P = .077$).
- Treatment time was shorter (23.4 hours vs 55.4 hours; $P < .001$), and the rt-PA dose was lower (33.4 mg vs 59.3 mg, $P = .009$) with ISPMT.
- Bleeding complications occurred in 5% of patients who underwent CDT alone and in 5% of the patients treated by ISPMT(the same)




BALLOON
ASPIRATION
BALLOON

- A single-center prospective registry found that US-assisted CDT in acute iliofemoral (87 patients) achieved high rates of venous patency, was rarely associated with bleeding, and that only 6% of patients had PTS at 1 year.94
- This new evidence has not led to a change in our recommendation for the use of CDT in patients with DVT. Although the quality of the evidence has improved, the overall quality is still low because of very serious imprecision.

Unchanged from AT9, we propose that the 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 .

Because the balance of risks and benefits with CDT is uncertain, we consider that anticoagulant therapy alone is an acceptable alternative to CDT in all patients with acute DVT who **do not have** impending venous gangrene.

Phlegmasia cerulea dolens

(literally: *painful blue edema*) is an uncommon severe form of deep venous thrombosis which results from extensive thrombotic occlusion (blockage by a thrombus) of the major and the collateral veins of an extremity. it is characterized by sudden severe pain, swelling, cyanosis and edema of the affected limb. There is a high risk of massive pulmonary embolism, even under anticoagulation. Foot gangrene may also occur. An underlying malignancy is found in 50% of cases. Usually, it occurs in those afflicted by a life-threatening illness.

- **Sever leg pain, swelling, cyanosis, edema.**
- **Venous gangrene**
- **Compartment syndrome.**
- **circulation collapse and shock .**
- **PE.**

TABLE 15] Risk Factors for Bleeding With, and Contraindications to Use of, Thrombolytic Therapy (Both Systemic and Locally Administered)

Major Contraindications[a]
Structural intracranial disease
Previous intracranial hemorrhage
Ischemic stroke within 3 mo
Active bleeding
Recent brain or spinal surgery
Recent head trauma with fracture or brain injury
Bleeding diathesis
Relative contraindications[b]
Systolic BP >180
Diastolic BP >110
Recent bleeding (nonintracranial)
Recent surgery
Recent invasive procedure
Ischemic stroke more than 3 mo previously
Anticoagulated (eg, VKA therapy)
Traumatic cardiopulmonary resuscitation
Pericarditis or pericardial fluid
Diabetic retinopathy
Pregnancy
Age >75 y
Low body weight (eg, <60 kg)
Female
Black race

Operative Venous Thrombectomy

- attention to operative detail, removal of all thrombus, and correction of underlying lesions, as well as maintenance of therapeutic Anticoagulation postoperatively, are crucial.
- Pooled data from a number of contemporary reports on iliofemoral venous thrombectomy indicate that the early and long-term patency rate of the iliofemoral venous segment is 75% to 80% versus 30% in patients treated by anticoagulation alone.
- Femoropopliteal venous valve function is preserved in the majority of patients

BOX 52-1

Overview of the Technique of Contemporary Venous Thrombectomy

1. Identify the cause of the extensive venous thromboembolic process
   - Complete thrombophilia evaluation
   - Rapid CT scan of the chest, abdomen, and pelvis
2. Define the full extent of the thrombus
   - Venous duplex examination
   - Contralateral iliocavagram, MRV, or spiral CT
3. Prevent pulmonary embolism (numerous techniques)
   - Anticoagulation
   - Vena caval filter (if nonocclusive caval clot)
   - Balloon occlusion of the vena cava during thrombectomy
   - Positive end-expiratory pressure during thrombectomy
4. Perform complete thrombectomy
   - Iliofemoral (vena cava) thrombectomy
   - Infrainguinal venous thrombectomy (if required)
5. Ensure unobstructed venous inflow to and outflow from the thrombectomized iliofemoral venous system
   - Infrainguinal venous thrombectomy (if required)
   - Correct iliac vein stenosis (if present)
6. Prevent recurrent thrombosis
   - Arteriovenous fistula
   - Continuous therapeutic anticoagulation
   - Catheter-directed postoperative anticoagulation (if infrainguinal venous thrombectomy is required)
   - Extended oral anticoagulation

MRV, Magnetic resonance venography.

Thrombolytic Therapy in Patients With Upper Extremity DVT

- 27. (UEDVT) that involves the **axillary or more proximal** veins, we **suggest** anticoagulant therapy alone over thrombolysis (Grade 2C).

Remarks: Patients who

- (i) are most likely to benefit from thrombolysis
- (ii) have access to CDT;
- (iii) attach a high value to prevention of PTS; and
- (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.
- 28. In patients with UEDVT who undergo thrombolysis, we recommend the **same intensity and duration** of anticoagulant therapy as in patients with UEDVT who do not undergo thrombolysis (Grade 1B).

The AT9 recommendation was based on

- (1) **mostly retrospective** observational studies suggesting that thrombolysis could improve short- and long-term venous patency, but a lack of data about whether thrombolysis reduced PTS of the arm;
- (2) **occasional reports** of bleeding in patients with UEDVT who were treated with thrombolysis, and clear evidence that thrombolysis increases bleeding in other settings; and
- (3) **recognition** that, compared to anticoagulation alone, thrombolytic therapy is complex and costly

We suggest that thrombolysis is most likely to be of benefit in patients who meet the following criteria:

- **Severe** symptoms; symptoms for **<14 days**
- thrombus involving most of **the subclavian vein and the axillary vein**;;
- Good functional status; life expectancy of $1 year; and
- **low risk** for bleeding.

We also suggested CDT over systemic thrombolysis to reduce the dose of thrombolytic drug and the risk of bleeding.

There is new moderate quality evidence that CDT can reduce PTS of the leg and that systemic thrombolysis increases bleeding in patients with acute PE,

and **low-quality evidence** that CDT can accelerate breakdown of acute PE. This evidence has indirect bearing on thrombolysis in patients with UEDVT, but it has not changed the overall quality of the evidence or our recommendations for use of thrombolysis in these patients

What if my patient stops anticoagulation?

- Aspirin is NOT a reasonable alternative to anticoagulation for extended therapy
  - Much less effective at preventing recurrent VTE
- However, aspirin is better than nothing (Grade 2B)

Aspirin for Extended Treatment of VTE

- *12. In patients with an **unprovoked proximal DVT or PE** who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B).

Remarks: Because aspirin is expected to be much less effective at preventing recurrent VTE than anticoagulants, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience.

- Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.

- two randomized trials have compared aspirin with placebo for the prevention of recurrent VTE in patients with a first unprovoked proximal DVT or PE who have completed 3 to 18 months of anticoagulant therapy.
- These trials provide moderate-quality evidence that extended aspirin therapy reduces recurrent VTE by about one-third. In these trials, the benefits of aspirin outweighed the increase in bleeding, which was not statistically significant
- Extended anticoagulant therapy is expected to reduce recurrent VTE by more than 80% and extended NOAC therapy may be associated with the same risk of bleeding as aspirin
- Based on indirect comparisons, we expect the net benefit of extended anticoagulant therapy in patients with unprovoked VTE to be substantially greater than the benefits of extended aspirin therapy.49
- Consequently, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin (may also include reductions in arterial thrombosis and colon cancer) that needs to be balanced against aspirin's risk of bleeding and inconvenience.

Compression Stocking to Prevent PTS

- *18. In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).
- Remarks: This recommendation focuses on **prevention** of the chronic complication of PTS and not on the treatment of symptoms.
- For patients with acute or chronic symptoms, a trial of graduated compression stockings is often justified.

AT9

- AT9 suggested routine use of graduated compression stockings for 2 years after DVT to reduce the risk of PTS.
- That recommendation was mainly based on findings of two small, single-center, randomized trials in which patients and study personnel were not blinded to stocking use (no placebo stocking).
- The quality of the evidence was moderate because of risk of bias resulting from a lack of blinding of an outcome (PTS) that has a large subjective component and because of serious imprecision of the combined findings of the two trials

- Since AT9, a much larger multicenter, **placebo-controlled trial** at low risk of bias found that routine use of graduated compression stockings did not reduce PTS or have other important benefits.
- Based on this trial, we now suggest that graduated compression stockings not be used routinely to prevent PTS and consider the quality to the evidence to be moderate

- The same study found that routine use of graduated compression stockings did not reduce leg pain during the 3 months after DVT diagnosis
- This finding, however, does not mean that graduated compression stockings will not reduce acute symptoms of DVT or chronic symptoms in those **who have already developed PTS**.

Pulmonary embolism

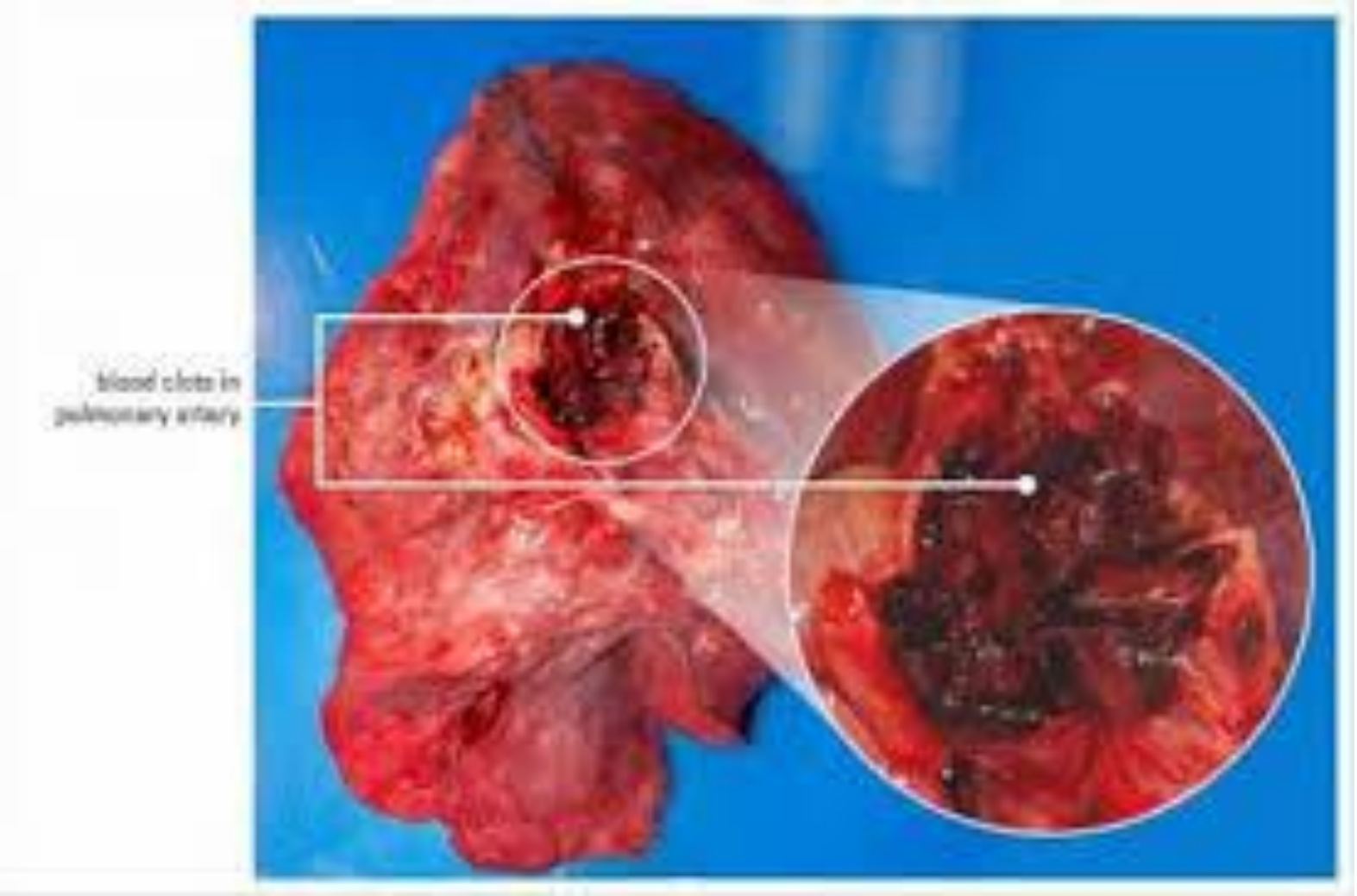
- In association with acute DVT, the majority of pulmonary emboli may be clinically silent. In patients presenting with symptomatic DVT, 50% to 80% have evidence of asymptomatic PE.
- Conversely, in those presenting with symptomatic PE, asymptomatic DVT can be demonstrated in approximately 80% of the cases.
- Approximately **90%** of thromboemboli arise from the lower extremity veins, and inadequate treatment of proximal lower extremity venous thrombosis is associated with a 20% to 50% risk of clinically significant recurrent thromboembolism.

Wells score

Criteria	Points
Clinical signs/symptoms of DVT	3
PE is most likely diagnosis	3
Tachycardia (>100 bpm)	1.5
Immobilization/surgery in previous 4 weeks	1.5
Prior DVT/PE	1.5
Hemoptysis	1
Active malignancy (trt w/in 6 month)	1

Low Risk	**Intermediate risk**	**High risk**
< 2 points	2-6 points	>6 points

PE unlikely	**PE Likely**
0-4 points	>4 points


blood clots in
pulmonary artery

- Modern imaging with computed tomography has revealed asymptomatic PE to be found in 1.5% of scans done for a reason other than suspected PE.
- In those with malignant disease undergoing staging the incidence of asymptomatic PE found on computed tomography was **3.3%**, whereas the overall incidence of VTE was found to be 6.3%.315
- Symptomatic manifestation of PE may depend on the patient's underlying **cardiopulmonary reserve** more than on the amount of the pulmonary circulation occluded.

Whether to Anticoagulate Subsegmental PE

- *19. (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a
- (i) **low risk for recurrent VTE** we suggest clinical surveillance over anticoagulation (Grade 2C) or
- (ii) high risk for recurrent VTE ,we suggest anticoagulation over clinical surveillance (Grade 2C).

Remarks: Ultrasound (US) imaging of the deep veins of both legs should be done to exclude proximal DVT.

- Clinical surveillance can be supplemented by serial US imaging of the proximal deep veins of both legs to detect evolving DVT
- Patients and physicians are more likely to choose for clinical surveillance over anticoagulation if there is good cardiopulmonary reserve or a high risk of bleeding.

why

- Subsegmental PE refers to PE that is confined to the subsegmental pulmonary arteries. Whether these patients should be treated, a question that was not addressed in AT9, has grown in importance because **improvements in CT pulmonary angiography** have increased how often subsegmental PE is diagnosed (ie, from approximately 5% to more than 10% of PE).

There is uncertainty whether these patients should be anticoagulated for two reasons.

- First, because the abnormalities are small, a diagnosis of subsegmental PE is more likely to be a false-positive finding than a diagnosis of PE in the segmental or more proximal pulmonary arteries.
- Second, because a true subsegmental PE is likely to have arisen from a small DVT, the risk of progressive or recurrent VTE without anticoagulation is expected to be lower than in patients with a larger PE

- Our literature search did not identify any randomized trials in patients with subsegmental PE.,
- however, There is high-quality evidence for the efficacy and safety of anticoagulant therapy in patients with **larger PE**, and this is expected to apply similarly to patients with subsegmental PE.1
- Whether the risk of progressive or recurrent VTE is high enough to justify anticoagulation in patients with subsegmental PE is **uncertain**

- The AT10 panel endorsed that, if no anticoagulant therapy is an option, patients with subsegmental PE should have bilateral US examinations to exclude proximal DVT of the legs.
- DVT should also be excluded in **other high-risk locations**, such as in upper extremities with central venous catheters.
- If DVT is detected, patients require anticoagulation.
- If DVT is not detected, there is uncertainty whether patients should be anticoagulated.
- If a decision is made not to anticoagulate, there is the option of doing one or more follow-up US examinations of the legs to **detect (and then treat**) evolving proximal DVT.

DIAGNOSIS

- Serial testing for proximal DVT has been shown to be a safe management strategy in patients with suspected PE who have non diagnostic ventilation-perfusion scans, many of whom are expected to have subsegmental PE.
- We suggest that a diagnosis of subsegmental PE is more likely to be correct (ie, a **true positive) if**:
- (1) the CT pulmonary angiogram is of high quality with good opacification of the distal pulmonary arteries;
- (2) there are multiple intraluminal defects;
- (3) defects involve more proximal subsegmental arteries (ie, are larger);
- (4) defects are seen on more than one image;
- (5) defects are surrounded by contrast rather than appearing to be adherent to the pulmonary artery walls;
- (6) defects are seen on more than one projection;
- (7) patients are symptomatic, as opposed to PE being an incidental finding;
- (8) there is a high clinical pretest probability for PE; and
- (9) D-dimer level is elevated, particularly if the increase is marked and otherwise unexplained.

In addition to whether or not patients truly have subsegmental PE, we consider the following to be **risk factors for recurrent or progressive VTE if patients are not anticoagulated**—patients who: are

- hospitalized or have reduced mobility for another reason;
- have active cancer (particularly if metastatic or being treated with chemotherapy); or
- have no reversible risk factor for VTE such as recent surgery. Furthermore,
- a low cardiopulmonary reserve or marked symptoms that cannot be attributed to another condition favor anticoagulant therapy,

whereas a high risk of bleeding favors no anticoagulant therapy.

- The decision to anticoagulate or not is also expected to be sensitive to patient preferences.
- Patients who are not anticoagulated should be told to return for reevaluation if symptoms persist or worsen.
- The evidence supporting our recommendations is low quality because of indirectness and because there is limited ability to predict which patients will have VTE complications without anticoagulation.

Treatment of Acute PE Out of the Hospital

- *20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (eg, after the first 5 days of treatment) (Grade 2B).

- Treatment of acute PE with a NOAC that does not require initial heparin therapy (eg, rivaroxaban, apixaban) facilitates treatment without hospital admission.

Consistent with AT9, we suggest that patients who satisfy all of the following criteria are suitable for treatment of acute PE out of the hospital:

- (1) clinically stable with good cardiopulmonary reserve;
- (2) no contraindications such as recent bleeding, severe renal or liver disease, or severe thrombocytopenia (ie, <70,000/mm3);
- (3) expected to be compliant with treatment; and
- (4) the patient feels well enough to be treated at home.

Clinical decision rules such as the **Pulmonary Embolism Severity Index** (PESI), either the original form with score <85 or the simplified form with score of 0, can help to identify low-risk patients who are suitable for treatment at home

- However, we consider clinical prediction rules as aids to decision making and do not require patients to have a **pre**defined score (eg, low-risk PESI score) to be considered for treatment at home.
- Similarly, although we do not suggest the need for routine assessment in patients with acute PE, we agree that the presence of right ventricular dysfunction or increased cardiac biomarker levels should discourage treatment out of the hospital

- Patients presenting with PEs can be broadly classified into three main groups:
- (1) patients with PEs without hemodynamic instability or evidence of right heart strain on echocardiography;
- (2) patients with submassive PEs who have central thromboembolic occlusion causing right ventricular strain without systemic hypotension; and
- (3) patients with massive PEs who have systemic hypotension in addition to right heart failure. A
- lthough systemic anticoagulation is the preferred treatment modality for the first group of patients, it is estimated that **30% to 50%** of patients with PEs have evidence of right heart strain (submassive PE).60
- Mortality among patients with submassive PEs is higher than the first group of patients.
- Over the long term, these patients have a higher incidence of chronic thromboembolic pulmonary hypertension.
- Massive PE is defined by systemic hypotension (systolic blood pressure <90 mm Hg), a drop in systolic blood pressure of more than 40 mm Hg, syncope, or cardiac arrest.
- Ninety-day mortality among this group of patients is almost 50%.

Systemic Thrombolytic Therapy for PE

- 21. **with hypotension** (eg, systolic BP <90 mm Hg for 15 min)) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2B).
- *22. In most patients with acute PE **not associated with hypotension**, we **recommend against systemically** administered thrombolytic therapy (Grade 1B).
- *23. In selected patients with acute PE **who deteriorate after** starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

Remarks: Patients with PE and without hypotension who have severe symptoms or marked cardiopulmonary impairment should be monitored closely for deterioration.

- Development of hypotension suggests that thrombolytic therapy has become indicated. Cardiopulmonary deterioration (eg, symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers) that has not progressed to hypotension may also alter the risk-benefit assessment in favor of thrombolytic therapy in patients initially treated with anticoagulation alone.

- The more severe and persistent the hypotension, and the more marked the associated features of shock and myocardial dysfunction or damage, the more compelling the indication for systemic thrombolytic therapy
- patients with PE without hypotension include a broad spectrum of presentations. **At the mild end of the spectrum** are those who have minimal symptoms and minimal cardiopulmonary impairment. As noted in the section "Setting for initial anticoagulation for PE," many of these patients can be treated entirely at home or can be discharged after a brief admission.
- **At the severe end of the spectrum** are those with severe symptoms and more marked cardiopulmonary impairment (even though systolic BP is >90 mm Hg). In addition to clinical features of cardiopulmonary impairment (eg, heart rate, BP, respiratory rate, jugular venous pressure, tissue hypoperfusion, pulse oximetry), they may have evidence of right ventricular dysfunction on their CT pulmonary angiogram or on echocardiography, or evidence of myocardial damage as reflected by increases in cardiac biomarkers (eg, troponins, brain natriuretic peptide).

- We suggest that patients **without hypotension** who are at the severe end of the spectrum be treated with **aggressive anticoagulation** and other supportive measures, and not with thrombolytic therapy. These patients need to be closely monitored to ensure that deteriorations are detected. Development of hypotension suggests that thrombolytic therapy has become indicated.
- **Deterioration that has not resulted in hypotension** may also prompt the use of thrombolytic therapy. For example, there may be a progressive increase in heart rate, a decrease in systolic BP (which remains >90 mm Hg), an increase in jugular venous pressure, worsening gas exchange, signs of shock (eg, cold sweaty skin, reduced urine output, confusion), progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers.
- We do not propose that echocardiography or cardiac biomarkers are measured routinely in all patients with PE, or in all patients with a non–low-risk PESI assessment. This is because, when measured routinely, the results of these assessments do not have clear therapeutic implications For example, we do not recommend thrombolytic therapy routinely for patients without hypotension who have right ventricular dysfunction and an increase in cardiac biomarkers.
- However, we encourage assessment of right ventricular function by echocardiography and/or measurement of cardiac biomarkers if, following clinical assessment, there is uncertainty about whether patients require more intensive monitoring or should receive thrombolytic therapy.

- It has long been established that systemic thrombolytic therapy accelerates resolution of PE as evidenced by more rapid lowering of pulmonary artery pressure, increases in arterial oxygenation, and resolution of perfusion scan defects, and that this therapy increases bleeding.
- **The net mortality benefit** of thrombolytic therapy in patients with acute PE, however, has been uncertain and depends on an individual patient's baseline (ie, without thrombolytic therapy) risk of dying from acute PE and risk of bleeding.
- Patients with the highest risk of dying from PE and the lowest risk of bleeding obtain **the greatest net benefit** from thrombolytic therapy.
- Patients with the lowest risk of dying from PE and the highest risk of bleeding obtain the least net benefit from thrombolytic therapy and are likely to be harmed.

- Since AT9, two additional small, randomized trials and a much larger trial have evaluated systemic thrombolytic therapy in about 1,200 patients with acute PE.
- The findings of these new studies have been combined with those of earlier studies in a number of meta-analyses.
- These new data, by reducing imprecision for estimates of efficacy and safety and the overall risk of bias, have increased the quality of the evidence from low to moderate for recommendations about the use of systemic thrombolytic therapy in acute PE

Pulmonary Embolism Thrombolysis trial

- Most of the new evidence comes from the Pulmonary Embolism Thrombolysis trial, which randomized 1,006 patients with PE and right ventricular dysfunction to tenecteplase and heparin or to heparin therapy alone (with placebo).
- The most notable findings of this study were that thrombolytic therapy prevented cardiovascular collapse but increased major (including intracranial) bleeding; these benefits and harms were finely balanced, with no convincing net benefit from thrombolytic therapy.
- An additional finding was that "**rescue thrombolytic therapy**" appeared to be of benefit in patients who developed cardiovascular collapse after initially being treated with anticoagulant therapy alone.

Management Implication of the Updated Evidence

The improved quality of evidence has not resulted in substantial changes to our recommendations because:

- (1) the new data support that the benefits of systemic thrombolytic therapy in patients without hypotension, including those with right ventricular dysfunction or an increase in cardiac biomarkers ("**intermediate-risk PE**"), are largely offset by the increase in bleeding; and
- (2) among patients without hypotension, it is still not possible to confidently identify those who will derive net benefit from this therapy.

Catheter-Based Thrombus Removal for the Initial Treatment of PE

- *24. treated with a thrombolytic agent, we **suggest systemic** thrombolytic therapy using a peripheral vein over CDT (Grade 2C).

Remarks: Patients who have a **higher risk of bleeding with systemic** thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy.

- *25. **with hypotension** and who have
- (i) a high bleeding risk,
- (ii) failed systemic thrombolysis, or
- (iii) shock that is likely to cause death before systemic thrombolysis can take effect (eg, within hours), if appropriate expertise and resources are available, we suggest **catheter assisted thrombus removal** over no such intervention (Grade 2C).

Remarks: Catheter-assisted thrombus removal refers to **mechanical interventions, with or without catheter directed thrombolysis.** if there is a high risk of bleeding

ADVANTAGES

- CDT, because it uses a lower dose of thrombolytic drug (eg, about one-third), is expected to cause less bleeding at remote sites (eg, intracranial, GI).
- CDT, however, may be as or more effective than systemic thrombolytic therapy for two reasons:

(1) it achieves a high local concentration of thrombolytic drug by infusing drug directly into the PE and

(2) thrombus fragmentation resulting from placement of the infusion catheter in the thrombus or additional maneuvers, or an increase in thrombus permeability from US delivered via the catheter, may enhance endogenous or pharmacologic thrombolysis.

- Thrombolytic therapy is usually infused over many hours or overnight. In emergent situations, systemic thrombolytic therapy can be given while CDT is being arranged, and active thrombus fragmentation and aspiration (see below) can be combined with CDT.
- An older randomized trial of 34 patients with massive PE found that infusion of recombinant tissue plasminogen activator into a pulmonary artery as opposed to a peripheral vein did not accelerate thrombolysis, but caused more frequent bleeding at the catheter insertion Site
- the AT10 panel **favored systemic thrombolytic therapy over CDT** because, compared with anticoagulation alone, there is a higher quality of evidence in support of systemic thrombolytic therapy than for CDT.

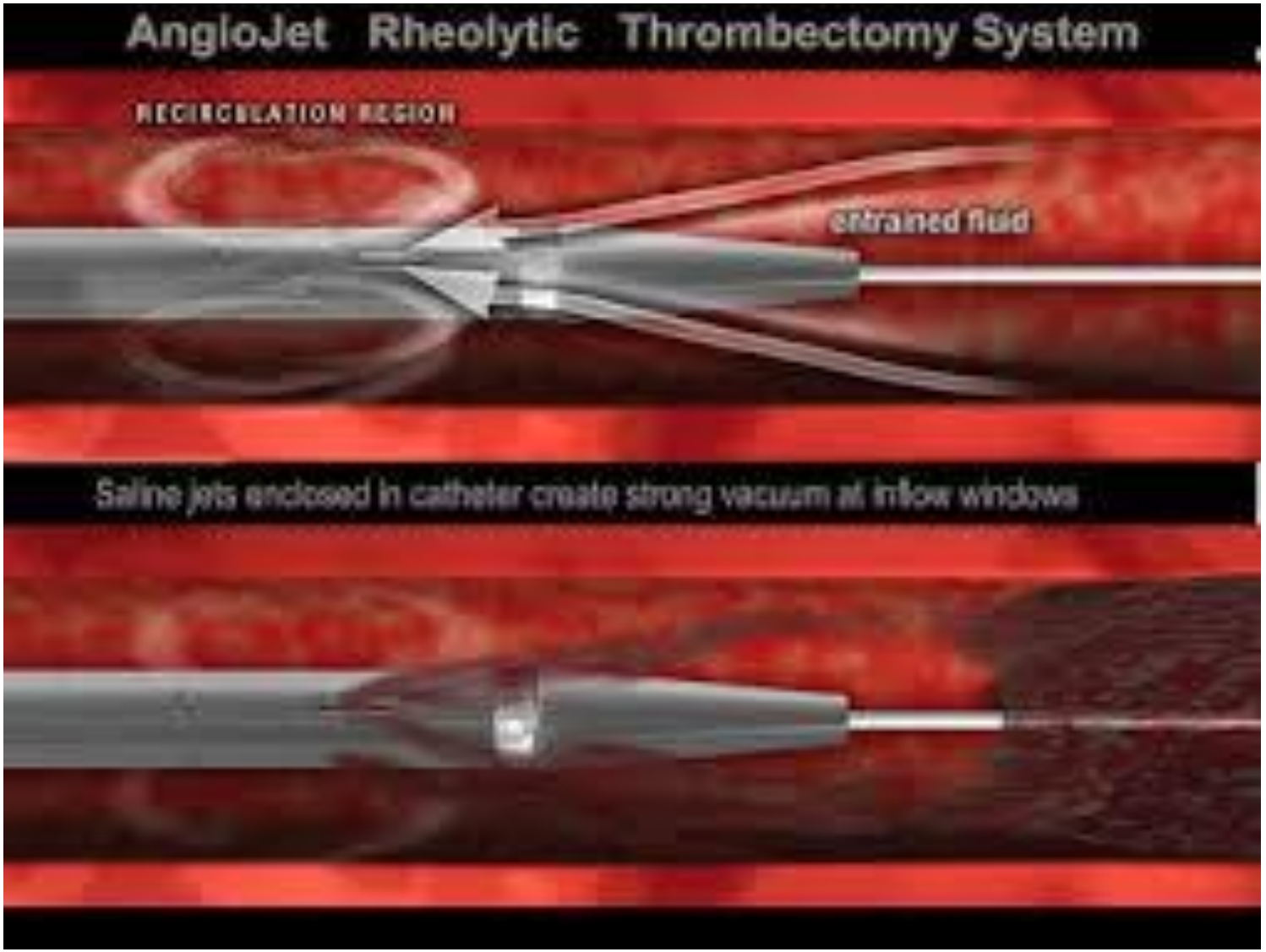
Catheter-Based Thrombus Removal Without Thrombolytic Therapy

- : Catheter-based mechanical techniques for thrombus removal involve thrombus fragmentation using various types of catheters, some of which are designed specifically for this purpose.
- Fragmentation results in distal displacement of thrombus, with or without suctioning and removal of some thrombus through the catheter.
- Mechanical methods alone are used when thrombus removal is indicated but there is a high risk of bleeding that precludes thrombolytic therapy.
- No randomized trial or prospective cohort studies have evaluated catheter-based thrombus removal of PE without thrombolytic therapy.
- Evidence for the use of CDT compared with anticoagulation alone, CDT compared with systemic thrombolytic therapy, and catheter-based treatment without thrombolytic therapy is **of low quality and our recommendations are weak.**

The basic concept

- underlying mechanical fragmentation of main pulmonary artery thrombus is that the cross-sectional area of the distal pulmonary arteries is larger than the main pulmonary arteries. Therefore, the simple disruption of large, central thrombi, which fragment into smaller thrombi and redistribute the occlusion from a main pulmonary artery to smaller pulmonary artery branches, improves pulmonary perfusion and reduces right ventricular overload.
- A recent metaanalysis122 reported that the **pigtail catheter** was used for fragmentation of massive PEs in nearly 70% of patients worldwide. Its use is likely due to its availability and lower cost.
- Schmitz-Rode et al123 described manual spinning of an angiographic pigtail catheter in the main pulmonary artery. Several authors have reported successful use of this technique in subsequent reports. An additional advantage to this technique is including **aspiration thrombectomy with an 8-Fr coronary catheter if needed.**
- Infusing the lytic agent directly into the thrombus and combining it with advanced endovascular techniques, such as rotational fragmentation and balloon angioplasty, further improves outcomes.

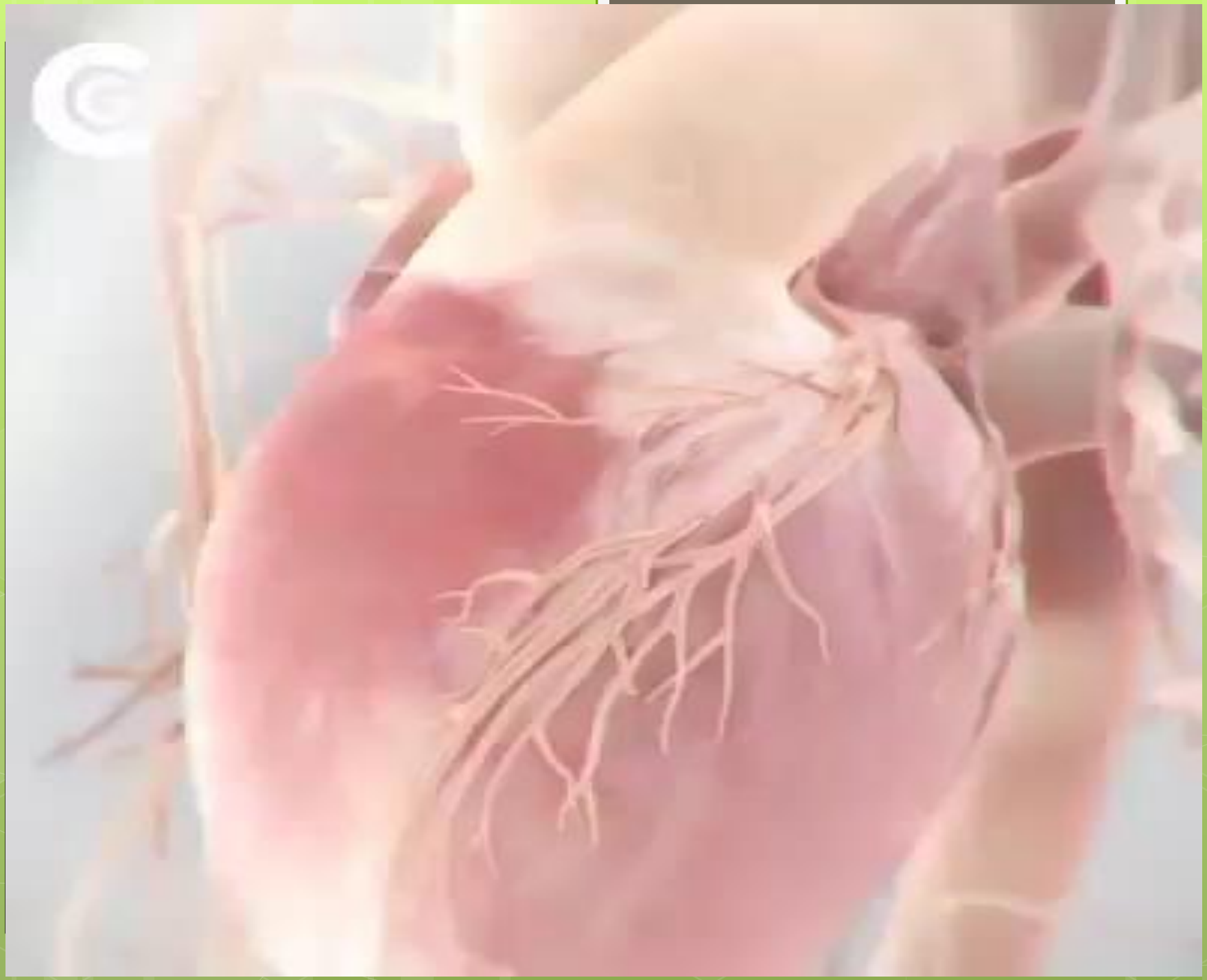
- **The AngioJet rheolytic thrombectomy system** (Possis Medical) is based on the Bernoulli principle. It generates a vacuum in the low-pressure zone behind a series of high pressure saline jets positioned at the tip of the catheter.
- These jets fragment the thrombus, some of which are then aspired in the vacuum zone.
- The use of the AngioJet for treating massive PE has been associated with several procedure-related complications.
- When used in the coronary and pulmonary vessels, the release of adenosine from the disrupted thrombus can cause arrhythmia and vasospasm, and worsen hypoxemia.
- Consequently, the (FDA) has issued a black-box warning regarding the use of this device in the pulmonary vasculature.


AngioJet Rheolytic Thrombectomy System
RECIRCULATION REGION
entrained fluid
Saline jets enclosed in catheter create strong vacuum at inflow windows

- **The Aspirex thrombectomy catheter** (Straub Medical AG, Wangs, Switzerland) uses a spiral rotating at 40,000 rpm to disrupt the thrombus, which can be aspirated via the side Port
- **The Amplatz-Helix thrombectomy catheter** (EV3) uses a rotating impeller that macerates thrombus and expels it through side holes. However, this device cannot be advanced over a wire.
- **The Hydrolyzer catheter** (Cordis, Warren, NJ), based on the Venturi principle, creates a vacuum by injecting saline at high pressure as the catheter passes through the thrombus.
- The catheter is pigtail shaped, and manual rotation fragments the thrombus that is aspirated through the side holes.

- **The EKOS ultrasound device** (EKOS Corp) uses multiple miniature ultrasound transducers in a low-energy application to dissociate fibrin strands.
- A lytic agent is then infused via side holes.
- A retrospective review of patients with massive PEs treated with the EKOS catheter demonstrated a significant reduction in the right-to-left ventricle ratio with low doses of rt-PA.
- The EKOS device is currently approved in Europe for the treatment of PE.

- As noted, all catheter-based technologies are based on the principle of fragmenting the large thrombus into smaller thrombi; an **inherent risk of this process is distal embolization, hemolysis, and release of vasoactive cytokines, which can worsen hypoxemia and right ventricular failure**.
- Given these risks, it would seem intuitive that the use of an endovascular device that can perform suction embolectomy of the entire thrombus would avoid the potential for complications. However, the use of larger devices undoubtedly requires larger sheath access, which has its own associated complications.
- **The Greenfield embolectomy catheter** (Medi-Tech/ Boston Scientific, Watertown, Mass) was a large diameter catheter with a suction tip at its end and a syringe to generate suction. Early experience with this catheter72 showed significant reductions in pulmonary artery pressures and improvements in cardiac output. Unfortunately, it was technically difficult to use, and good results could not be replicated.
- Renewed interest in endovascular suction embolectomy has resulted in the development of the **Angiovac catheter** (Angiodynamics, Latham, NY). It is approved by the FDA for removal of large thrombi. A funnel at the tip of the catheter is connected to a cardiopulmonary bypass system.
- The thrombus and blood are suctioned into the catheter and the blood is returned to the circulation via the cardiopulmonary bypass.
- Limitations include the need for large sheaths and/or the need for surgical cut-down.
- There are anecdotal reports of clinical success with the catheter, but no reports have been published of its uses in humans with iliofemoral DVT or massive PE.



Pulmonary Thromboendarterectomy for the Treatment of Chronic Thromboembolic Pulmonary Hypertension

- *26. In selected patients with (**CTEPH**) who are identified by an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).

Remarks: Patients with CTEPH should be evaluated by a team with expertise in treatment of pulmonary hypertension. Pulmonary thromboendarterectomy is often lifesaving and life-transforming.

- Patients with CTEPH who are not candidates for pulmonary thromboendarterectomy may benefit from othe mechanical and pharmacological interventions designed to lower pulmonary arterial pressure.

- Chronic thromboembolic pulmonary hypertension is associated with recurrent PE, younger age at onset, large perfusion defects, and idiopathic PE.
- PEs large enough to cause right ventricular dysfunction are associated with a 6-fold increase in hospital mortality and a 2.4-fold increase in 1-year mortality.

- The AT9 recommendation was based on case series that have shown marked improvements in cardiopulmonary status after thromboendarterectomy in patients with (CTEPH)
- Although additional case series have been reported, the quality of the evidence for thromboendarterectomy in patients with CTEPH has not improved.
- because of improvements in surgical technique, it is now often possible to remove organized thrombi from peripheral pulmonary arteries.
- In patients with inoperable CTEPH or persistent pulmonary hypertension after pulmonary thromboendarterectomy, there is new evidence from a randomized trial that pulmonary vasodilator therapy may be of benefit.
- For these reasons, we no longer identify central disease as a selection factor for thromboendarterectomy in patients with CTEPH, and we emphasize that patients with CTEPH should be assessed by a team with expertise in the evaluation and management of pulmonary hypertension.

Summary

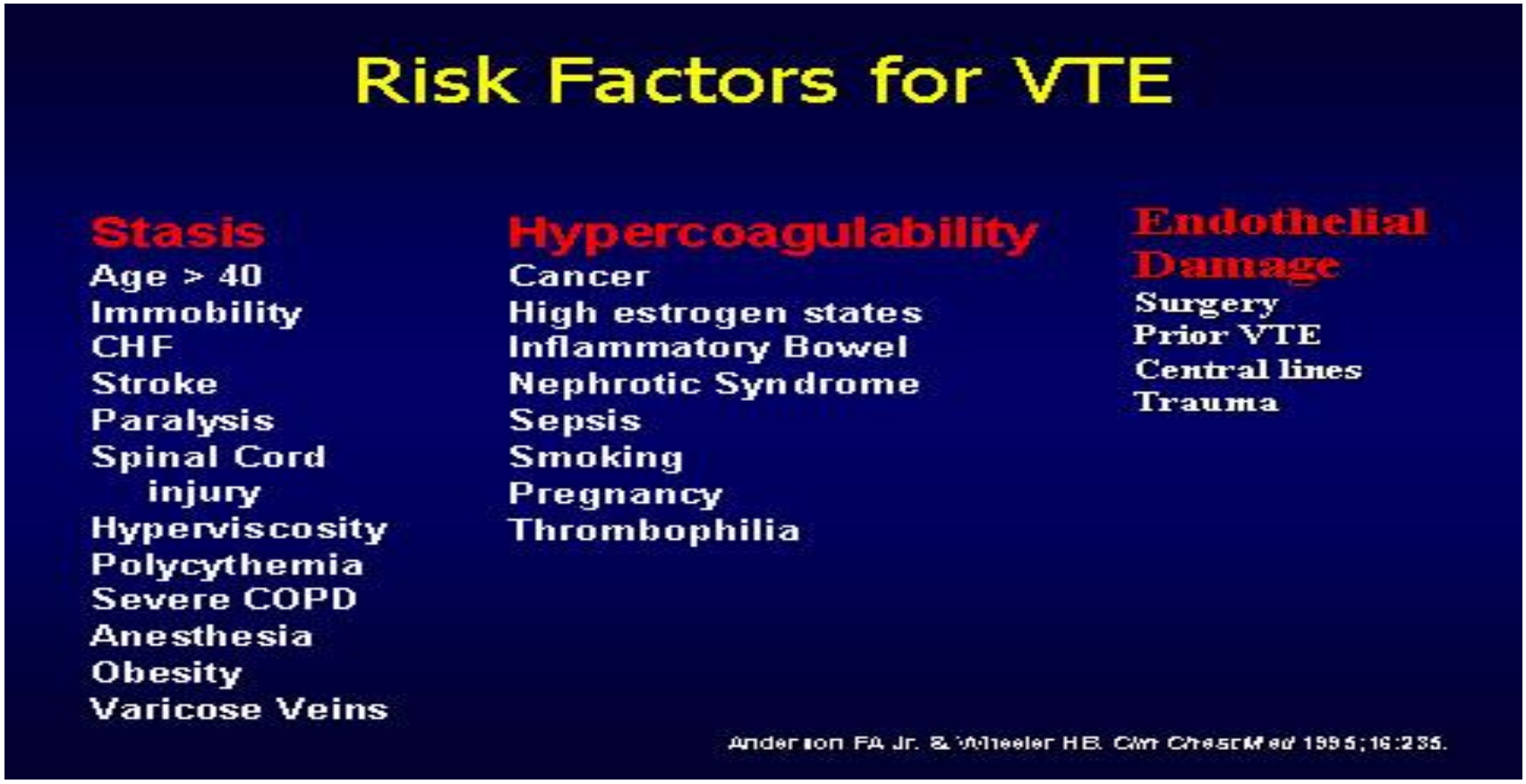
- NOACs are preferred over warfarin for anticoagulation
- **Except if VTE is cancer-associated**, then use enoxaparin
- Duration of therapy is usually 3 months, with **extended therapy based on risk factors for recurrent VTE**

- Of the 54 recommendations that are included in the 30 statements in this update, 20 (38%) are strong recommendations (Grade 1) and none is based on highquality (Grade A) evidence.
- The absence of high-quality evidence highlights the need for further research to guide VTE treatment decisions.
- As new evidence becomes available, these guidelines will need to be updated.
- Goals of our group and CHEST include transition to continually updated "**living guidelines**

References

- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy For VTE Disease: CHEST Guideline And Expert Panel Report. *CHEST*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.
- MKSAP 17

VTE prophylaxis



risk factors

- prior DVT/pulmonary embolism,
- prolonged immobilization or paralysis
- malignancy, major surgery (especially abdominal, hip and lower-extremity surgery),
- age over 40 years, and severe heart disease.
- hypercoagulable states that predispose to thrombosis.

deep venous thrombosis

not-pharmacological perioperative profilaxys

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- 52% of patients with DVT develop PE, most of which occur from the **proximal** venous segments of the lower extremities
- Patients with proximal DVT had a pulmonary embolism incidence of **66%,** whereas tibial thrombi had a 33% incidence
- **PTS** has been reported in 33–79% of patients following proximal DVT and 2–29% of patients with calf DVT.
- Masuda et al. reported valve reflux in 30% of individuals with calf DVT followed for 3 years. Furthermore, they reported that 23% of patients with calf DVT have ongoing pain and swelling of the affected extremity.
- Thus, proper prophylaxis, early diagnosis and appropriate therapy are of paramount importance in preventing the short- and long-term complications of DVT

available methods of DVT prophylaxis,

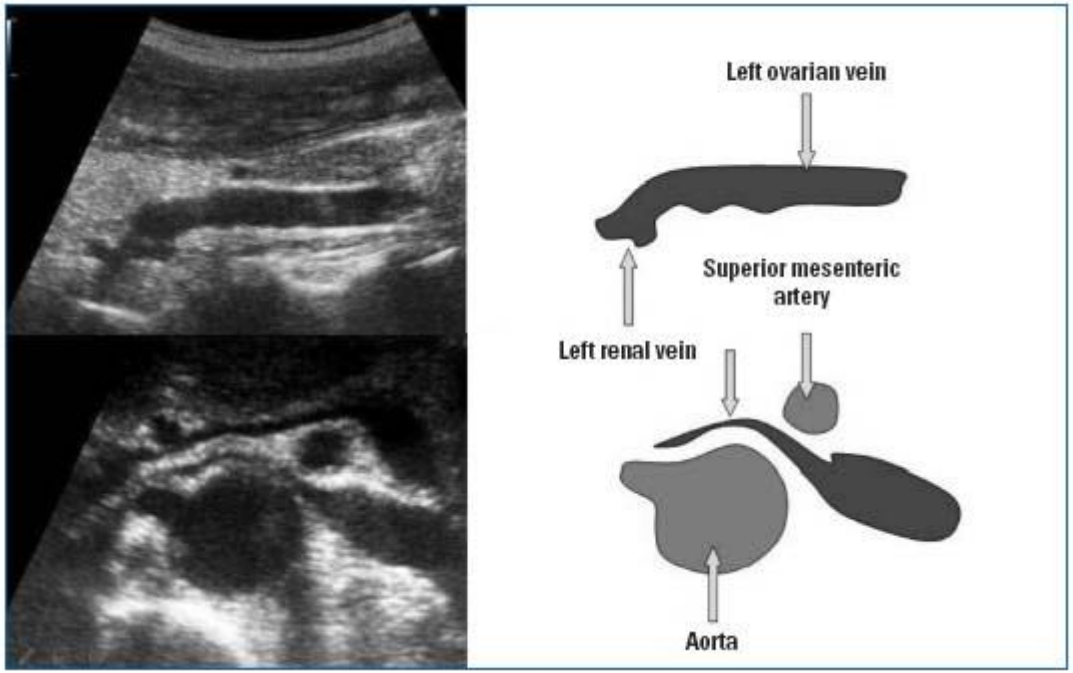
- LDUH and LMWH are the most effective in reducing DVT as assessed by FUT.
- LDUH was the first anti-thrombotic agent evaluated in early randomised studies. LDUH, dextran, IPC and graded elastic stockings also significantly reduce the incidence of postoperative DVT.

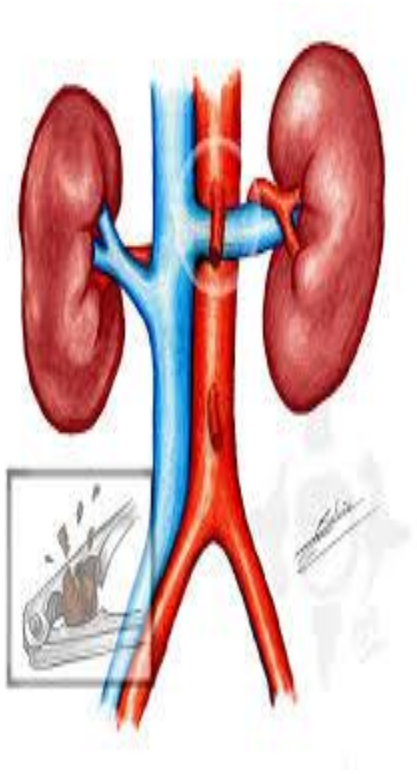
- **LDUH** given subcutaneously (5,000 U) every 8 or 12 h started preoperatively and continued postoperatively for 7 days has been shown to decrease the incidence of DVT from 25% to 8%.
- Moreover, these studies have shown a 50% reduction of fatal pulmonary embolism when patients are treated with LDUH.
- LMWH and LDUH have been shown to be equally effective in preventing DVT in general surgery patients
- Advantages of LMWH include improved bioavailability, once-daily dosing, and a lower incidence of HIT

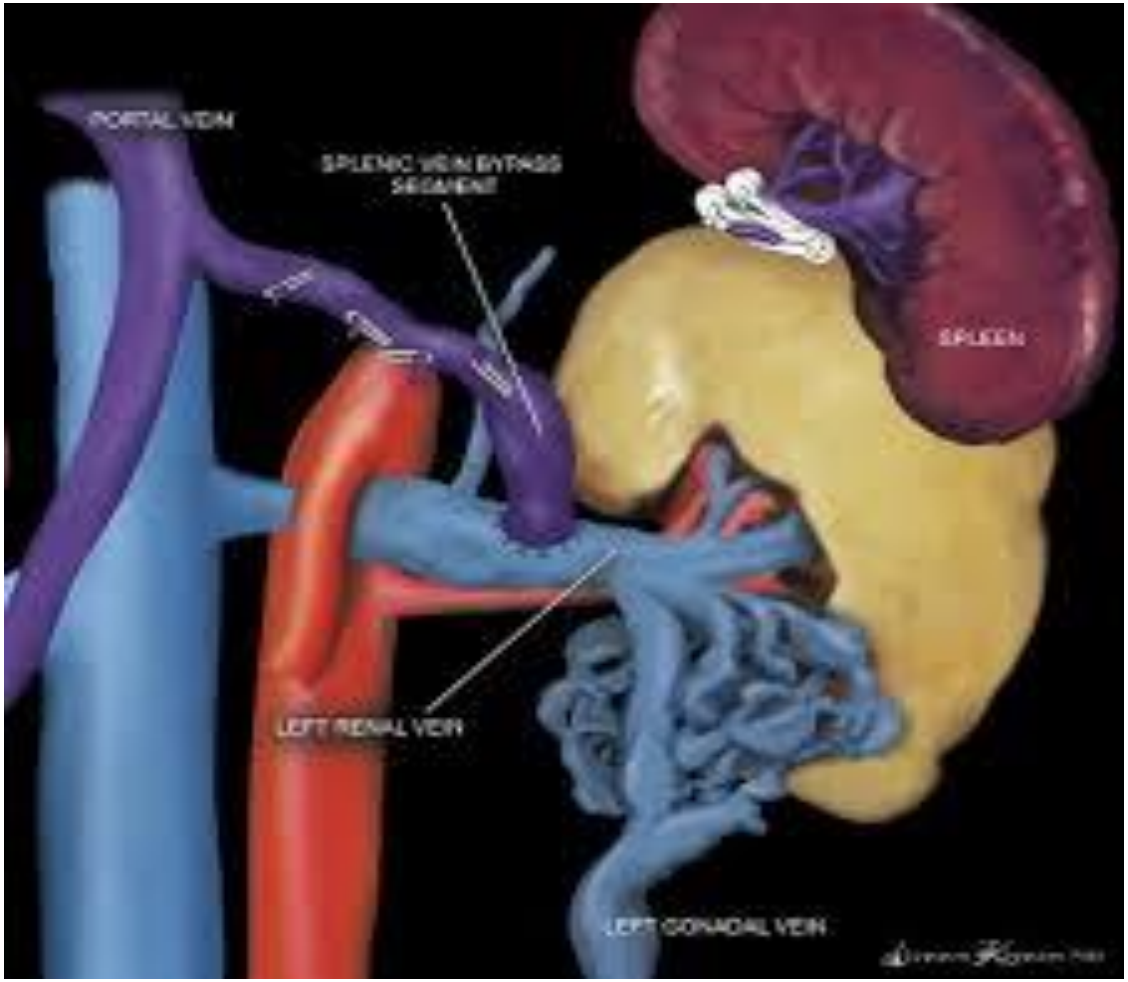
OTHERS

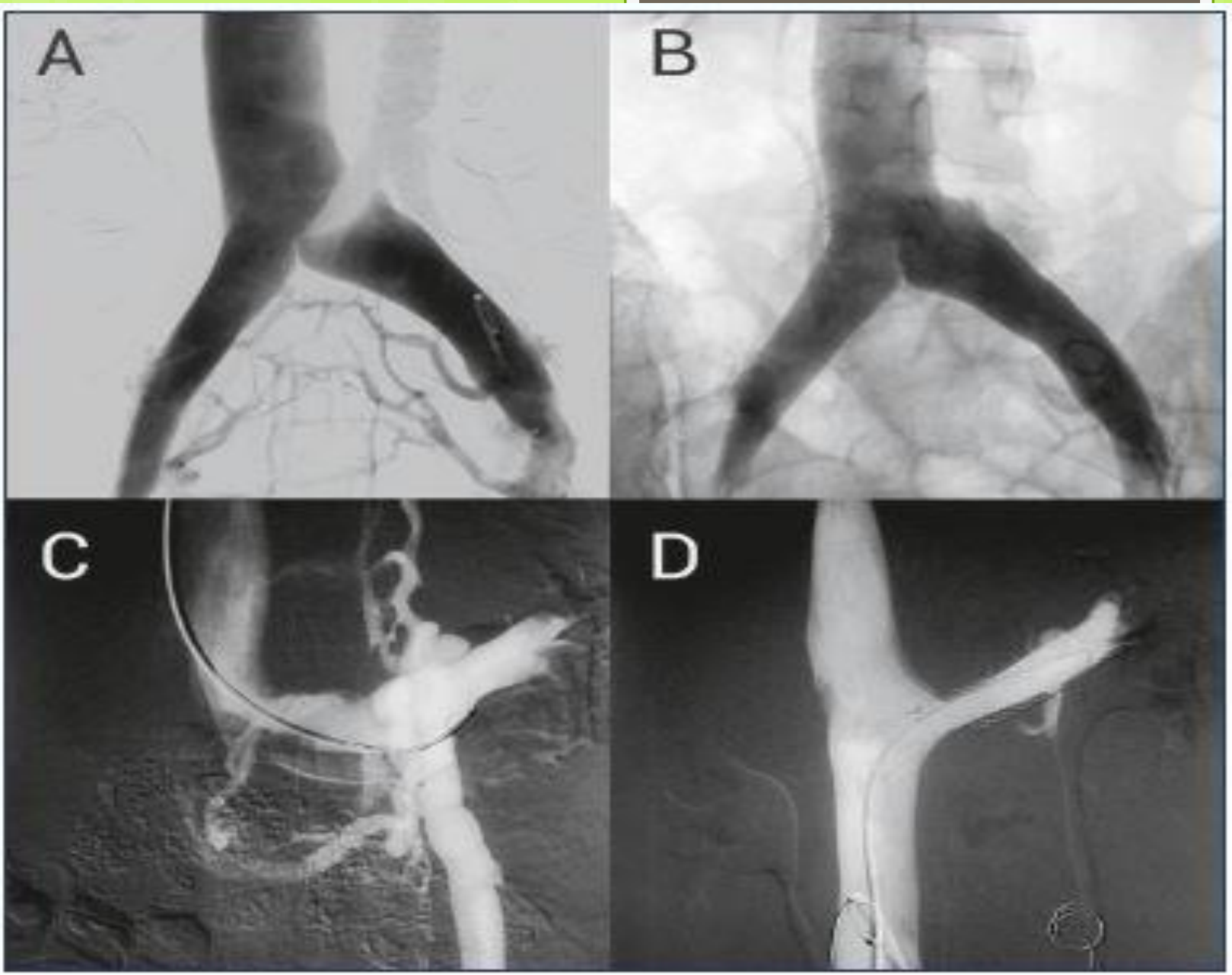
- **IPC** is an attractive method of DVT prophylaxis since there are no observed complications.
- This device provides intermittent compression lasting 10 s/min with insufflation pressures of 35–40 mmHg.
- In a trial comparing IPC with LDUH, both agents were effective in reducing lower-extremity DVT in high-risk patients.
- **Graded compression stockings** decrease the risk of DVT, but data are limited regarding the effect on the prevention of DVT and pulmonary embolism. There are no randomised trials on the use of these stockings alone in high-risk patients, although current recommendations suggest the use of more effective methods.
- Fifteen to 20% of patients will not receive benefit from elastic stockings because of their **leg shape or size**
- **Dextran** has not been shown to be as effective as either LMWH or LDUH in preventing DVT; however, it may reduce the incidence of pulmonary embolism.
- Disadvantages of dextran include its high price, risk of anaphylaxis, potential for volume overload, and need for intravenous access. It is also contraindicated in patients with impaired renal and cardiac function.

NUTcraker SYNDROMES



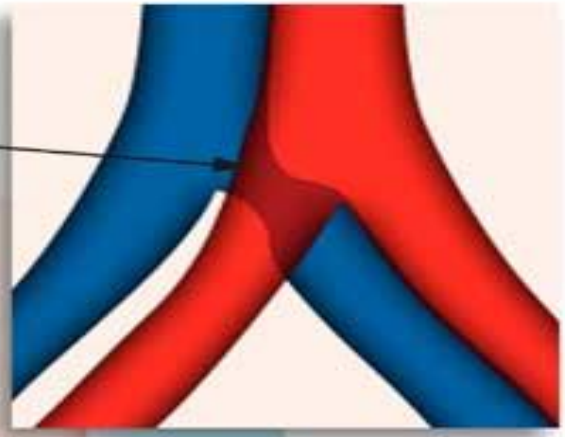


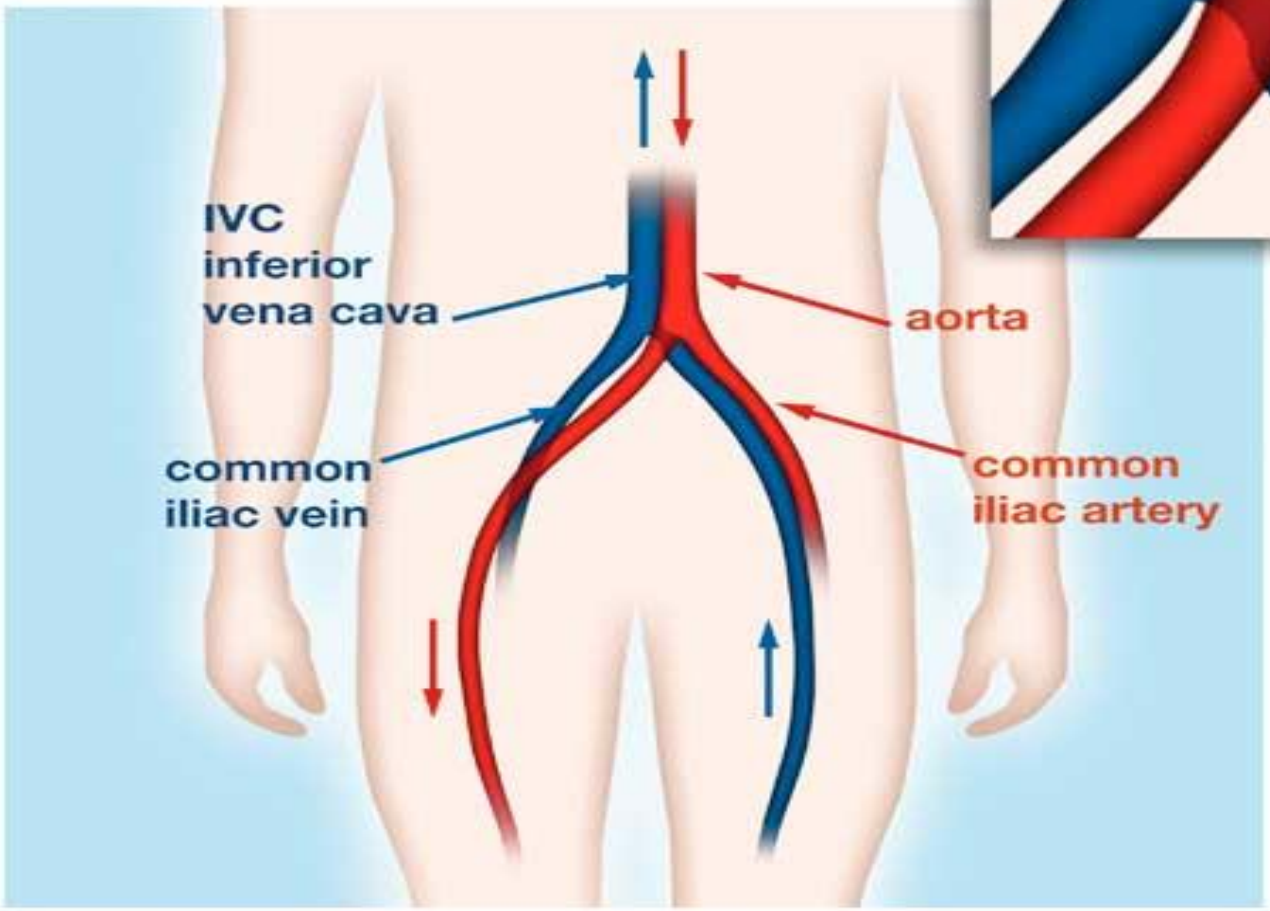

PORTAL VEIN
SPLENIC VEIN BYPASS
SPLEEN
LEFT RENAL VEIN
LEFT GONADAL VEIN


A
B
C
D

May-Thurner syndrome

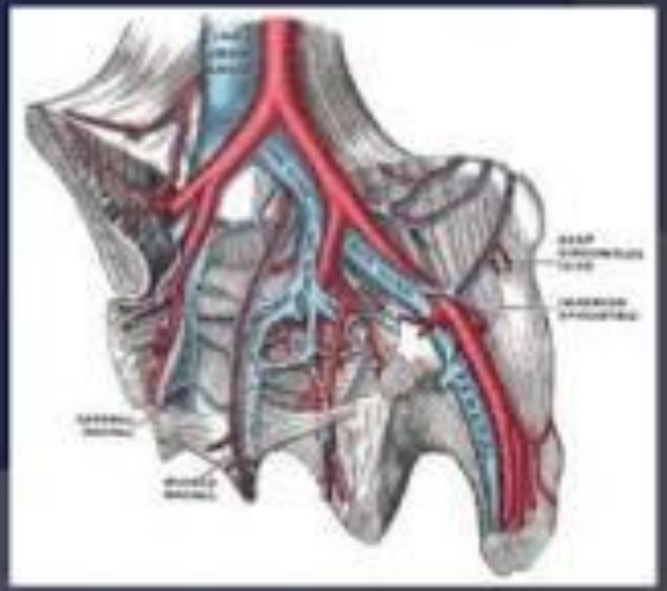
Narrowed left iliac vein
(by pressure from right iliac artery)





May-Thurner Syndrome

- (Cockett syndrome; iliocaval compression syndrome)
- Anatomical variant - Compression of Left common iliac vein by the Right common iliac artery
- DVT formation may result
- May be asymptomatic
- DX on CT or MR venogram
- May be missed on US



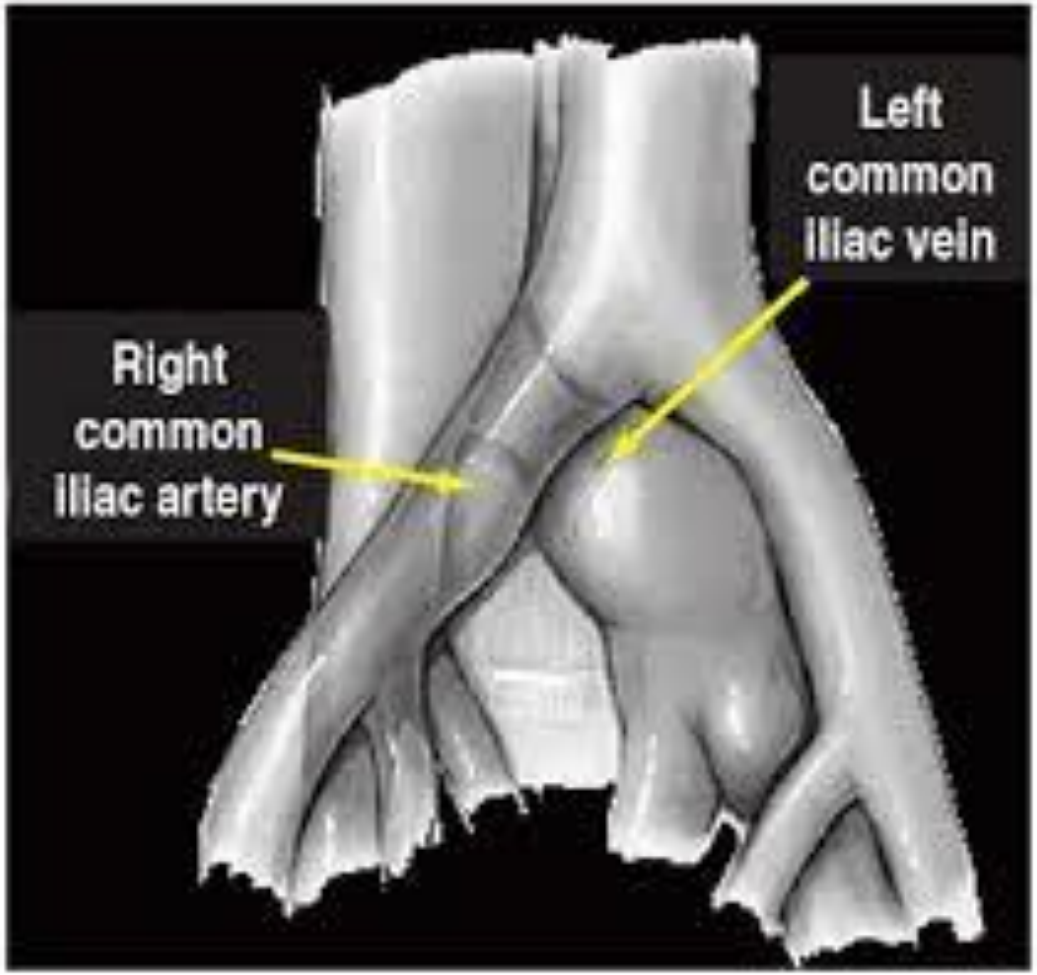


Figure 1. Illustration demonstrating the anatomic compression seen in May-Thurner syndrome.

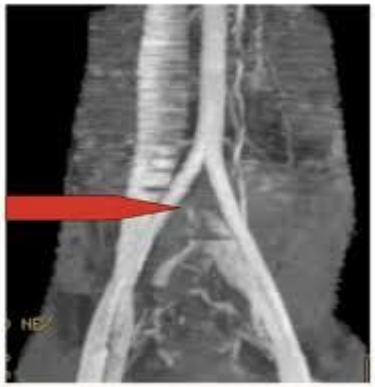
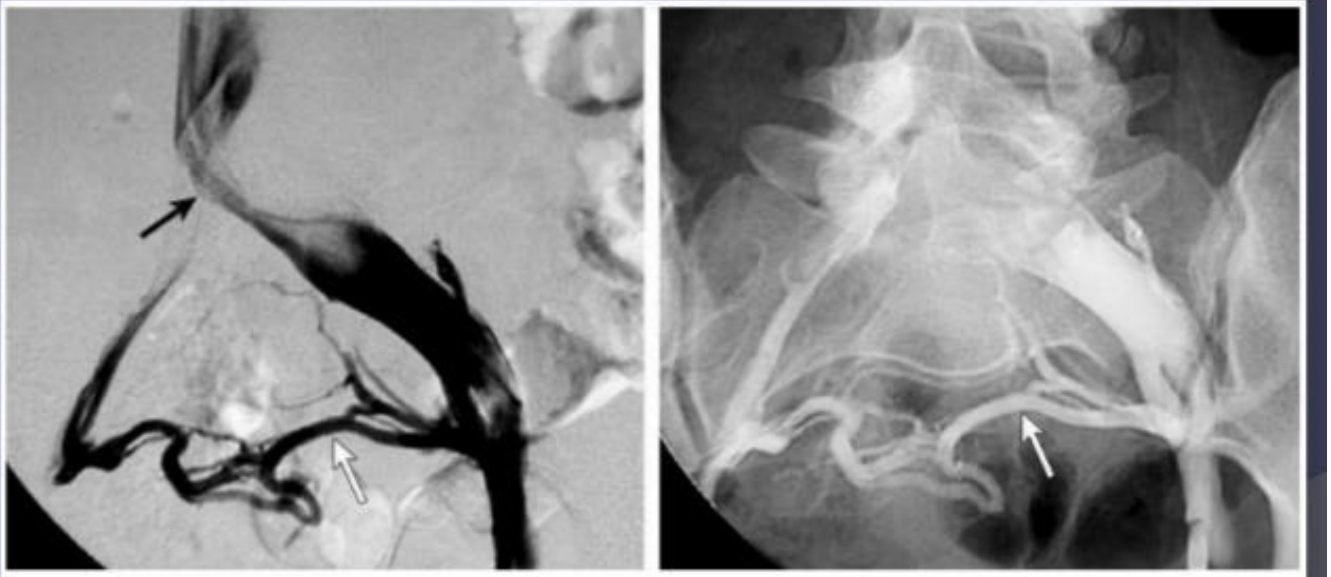


Figure 1. Severe narrowing of left common iliac vein from overlying right common iliac artery (arrow), on coronal magnetic resonance venography, consistent with May-Thurner syndrome or nonocclusive iliac vein lesion.

May-Thurner Syndrome



a. b.

Figure 2. (a) Subtracted and (b) nonsubtracted frontal venograms show left iliac veins. Note the compressed left common iliac vein (black arrow) and contralateral venous drainage via pelvic venous collaterals (white arrows).

Phlegmasia alba dolens

(also colloquially known as **milk leg** or **white leg**). Historically, it was commonly seen during pregnancy and in mothers who have just given birth. In cases of pregnancy, it is most often seen during the third trimester, resulting from a compression of the left common iliac vein against the pelvic rim by the enlarged uterus. Today, this disease is most commonly (40% of the time) related to some form of underlying malignancy.

- **Pale & cold.**
- **Decreased arterial pulse.**
- **Sudden or acute occlusion of iliac and femoral veins.**

- In a prospective observational study of anticoagulation for acute DVT, **iliofemoral DVT** was found to be the most powerful predictor of severe PTS (hazard ratio 2.23).8
- Labropoulos et al9 monitored venous pressures in patients with PTS after treatment for their acute DVT. They found that patients who were treated for iliofemoral DVT had the highest venous pressures. This confirmed previous observations that iliofemoral DVT patients treated by anticoagulation alone had ambulatory venous hypertension, with 40% demonstrating venous claudication and up to 15% developing venous ulceration within 5 years
- The morbidity of PTS escalates substantially with ipsilateral recurrence.
- A meta-analysis of outcomes after treatment for acute DVT demonstrated that recurrence occurs more commonly in patients with a large burden of thrombus

- Ambulatory venous pressure is linearly linked to the pathophysiologic changes observed with chronic venous disease, such as swelling, pigmentation, and lipodermatosclerosis.13
- Microcirculatory changes leading to dermal breakdown follow. The most severe postthrombotic morbidity is associated with the highest venous pressures, which occur in patients with both valvular incompetence and luminal venous obstruction.1
- Although valvular function can be reliably assessed with ultrasound by quantifying valve closure times, techniques are not yet available to assess the relative contribution of venous obstruction to the pathologic venous hemodynamics leading to clinical postthrombotic morbidity. Figure 52-1
- succinctly illustrates the difficulty of identifying even extensive venous obstruction, either hemodynamically or radiologically. Neither ascending phlebography performed and interpreted by a skilled radiologist nor the maximal venous outflow test performed in an accredited vascular laboratory identified abnormalities attributed to venous obstruction.

- It is evident that venous hemodynamics are adversely affected long before imaging techniques can detect obstruction.
- The inability to quantitate obstruction has led physicians to underappreciate its contribution to postthrombotic pathophysiology.
- Luminal venous obstruction causes the most severe forms of PTS. Therefore, treatment strategies for thrombus removal should be developed during the initial encounter with the patient, and if successful, can eliminate obstruction as part of the long-term pathophysiology and should significantly reduce the incidence of PTS.
- Investigators have found that distal valve incompetence develops in patients with persistent venous obstruction treated with anticoagulation alone, even when the distal veins are not initially involved with thrombus.17
- When spontaneous lysis occurred, defined as clot resolution within 90 days, valve function was frequently preserved.18
- These investigators also confirmed that the combination of valvular incompetence and venous obstruction was associated with the most severe postthrombotic morbidity

- Killewich et al,17 who demonstrated that persistent proximal obstruction leads to distal valve incompetence in veins not initially involved with thrombus, and that elimination of iliofemoral thrombosis maintains distal valve function.
- Pharmacomechanical techniques have been shown to improve outcomes compared with CDT using the drip technique alone.
- Pharmacomechanical techniques have shortened treatment times, reduced doses of lytic agentand reduced length of intensive care unit (ICU) and hospital stays

- Aziz and Comerota26 observed that patients with iliofemoral DVT treated with catheter-directed techniques appeared to have a low recurrence rate. Upon further analysis, the benefit was accrued in those patients who had successful thrombus removal, whereas those with the bulk of the thrombus remaining (unsuccessful lysis) had a significantly higher recurrence rate.
- Vogel et al34 addressed the issue of whether pharmacomechanical techniques compromised valve function, presumably due to valve injury. In a sequential analysis of CDT versus pharmacomechanical thrombolysis, there did not appear to be any adverse effect on valve function using pharmacomechanical techniques.
- The important observations were that valves functioned best in patients who had successful results. An interesting observation was that 35% of the veins in the noninvolved limbs had incompetent valves.