



VENOUS THROMBOEMBOLISM (VTE)

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■ EPIDEMIOLOGY

Venous thromboembolism (VTE) encompasses deep-venous thrombosis (DVT) and pulmonary embolism (PE) and causes cardiovascular death, chronic disability, and emotional distress. Hospitalizations in the United States have decreased for acute myocardial infarction (MI), heart failure, and stroke among Medicare beneficiaries, but PE hospitalizations increased

Pulmonary Embolism Mortality

PE-related mortality in the United States decreased from 6 per 100,000 in 2000 and plateaued at approximately 4.5 per 100,000 in 2017. In contrast, Europe's age-standardized annual PE-related mortality rate has continued to decrease linearly since 2000. In the United States, PE-related mortality is increasing among young and middle-aged adults.

Socioeconomic Status

Hospitalizations for MI, heart failure, and stroke declined in socioeconomically disadvantaged and nondisadvantaged communities. In contrast, PE hospitalizations increased in both disadvantaged and nondisadvantaged communities..

In contrast, mortality among patients hospitalized with PE was consistently higher in disadvantaged areas .

This finding may be due, in part, to poor outpatient follow-up and impeded access to anticoagulant medications.

Pulmonary Embolism Readmissions

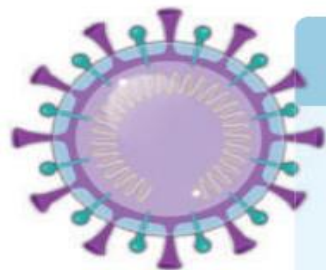
The 30-day all-cause readmission rate was 11%, and the 90-day all-cause readmission rate was 15%

The most common reason for readmission was recurrent PE, accounting for about 11% of readmissions within 30 days.

COVID-19

This viral illness was associated with a high incidence of DVT and PE. At autopsy, about one-fourth of PE patients with COVID had both macrovascular and microvascular PE.

Contributing etiologies included excessive inflammation with cytokine storm, platelet activation, endothelial dysfunction, and stasis



Sars-COV-2

A

Risk factors

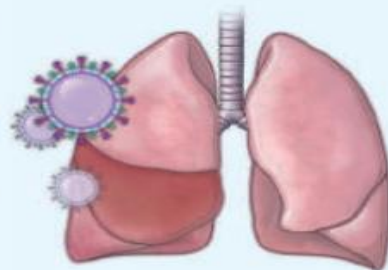
- Acute illness
- Bed-ridden, stasis
- Genetics
- Fever
- Diarrhea
- Sepsis
- Liver injury
- CKD
- COPD
- HF
- Malignancy

Inflammatory response → Endothelial dysfunction Superinfected

Tissue factor
↓TFPI

Lymphopenia

Inflammatory
cytokines
↑IL-6, CRP



B

Hemostatic abnormalities

- Pulmonary microthrombi
- Intravascular coagulopathy
- Myocardial injury
- ↑ Cardiac biomarkers



- ↑ D-dimer, FDPs, PT
- ↓ Platelets

C

Clinical outcomes



Venous thromboembolism



Myocardial infarction



Disseminated intravascular
coagulation

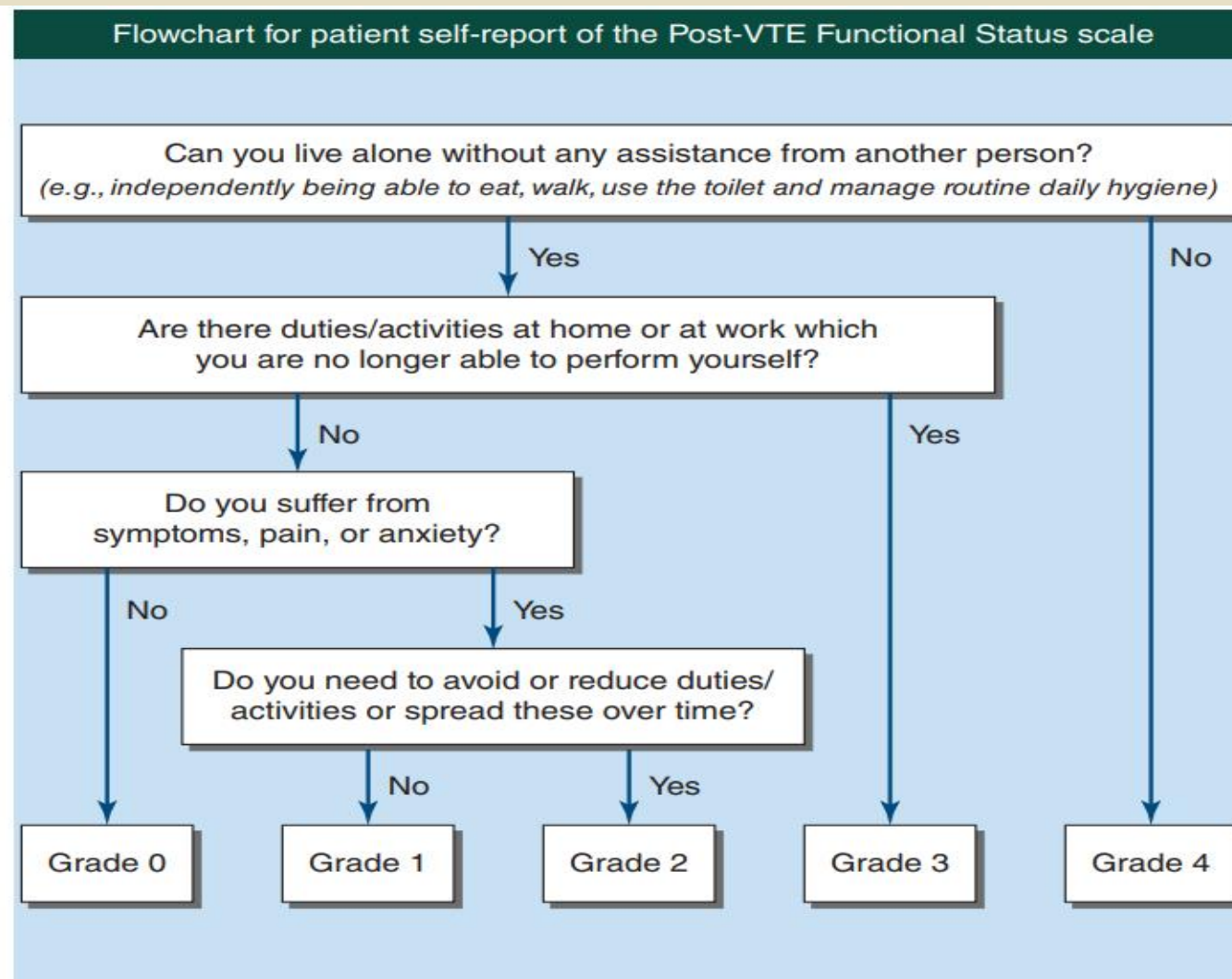
Postulated mechanisms of coagulopathy and pathogenesis of thrombosis

Long-Term Sequelae of PTE

With respect to quality of life, **about half** of PE patients report persistent dyspnea, fatigue, and reduced exercise capacity, and about **one-quarter** have persistent right ventricular dysfunction on echocardiogram. This constellation of findings is being recognized more frequently and is called the “post-PE syndrome”

A less frequent complication of PE is the development of chronic thromboembolic pulmonary hypertension (CTEPH), which usually causes breathlessness, especially with exertion.

PVFS scale grade		Description
0	No functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity. Symptoms, pain and anxiety are absent.
1	Negligible functional limitations	All usual duties/activities at home or at work can be carried out at the same level of intensity, despite some symptoms, pain, or anxiety.
2	Slight functional limitations	Some usual duties/activities at home or at work are carried out at a lower level of intensity or are occasionally avoided due to symptoms, pain, or anxiety.
3	Moderate functional limitations	Usual duties/activities at home or at work have been structurally modified (reduced) due to symptoms, pain, or anxiety.
4	Severe functional limitations	Assistance needed in activities of daily living due to symptoms, pain, or anxiety: nursing care and attention are required.
D	Death	Death occurred before the scheduled assessment.



Flow chart for patient self-report of the Post (VTE) Functional Status scale

Postthrombotic Syndrome

Postthrombotic syndrome (also known as *chronic venous insufficiency*) damages the venous valves of the leg and worsens quality of life by causing ankle or calf swelling and leg aching, especially after prolonged standing. In its most severe form, postthrombotic syndrome causes deep skin ulceration

**Skin ulceration in the
medial malleolus**
from postthrombotic
syndrome of the leg



■ **PATHOPHYSIOLOGY**

Inflammation

Inflammation takes center stage as a trigger of acute PE and DVT. Inflammation-related risk factors and medical illnesses are now linked as precipitants of VTE

TABLE 290-1 Inflammation-Linked Conditions That Can Trigger PE or DVT

Ulcerative colitis
Crohn's disease
Rheumatoid arthritis
Psoriasis
Diabetes mellitus, type 2
Obesity/metabolic syndrome
Hypercholesterolemia, especially elevated LDL cholesterol
Lipoprotein(a)
Pneumonia
Acute coronary syndrome
Acute stroke
Cigarette smoking
Sepsis/septic shock
Erythropoiesis-stimulating agents
Blood transfusion
Cancer

Abbreviations: DVT, deep-venous thrombosis; LDL, low-density lipoprotein; PE, pulmonary embolism.

Prothrombotic States

The two most common autosomal dominant genetic mutations are

- (1) **factor V Leiden**, which causes resistance to the endogenous anticoagulant, protein C,
- (2) **the prothrombin gene mutation**, which increases the plasma prothrombin concentration

Antithrombin, protein C, and protein S are naturally occurring coagulation inhibitors.

Deficiencies of these inhibitors are associated with VTE but are rare.

Antiphospholipid syndrome (APS) is an acquired (not genetic) thrombophilic disorder that predisposes to both venous and arterial thrombosis. Patients with APS often warrant lifetime anticoagulation, even if the initial VTE was provoked by trauma or surgery

Clinical Risk Factors

Common comorbid VTE risk factors include cancer, obesity, cigarette smoking, systemic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, long-haul air travel, air pollution, estrogen-containing contraceptives, pregnancy, the first 6–12 weeks postpartum, postmenopausal hormone replacement, surgery, and trauma.

A sedentary lifestyle is an increasingly prevalent risk factor. A Japanese study found that each 2 hours per day increment of television watching is associated with a 40% increased likelihood of fatal PE.

Polygenic Risk Scores

Ghouse and colleagues identified 93 risk loci, 62 of which were previously unreported. Many risk loci affected the coagulation cascade or platelet function.

A VTE *polygenic risk score (PRS)* enabled identification of both high- and low-risk individuals.

PRS improved individual risk prediction beyond that of genetic and clinical risk factors.

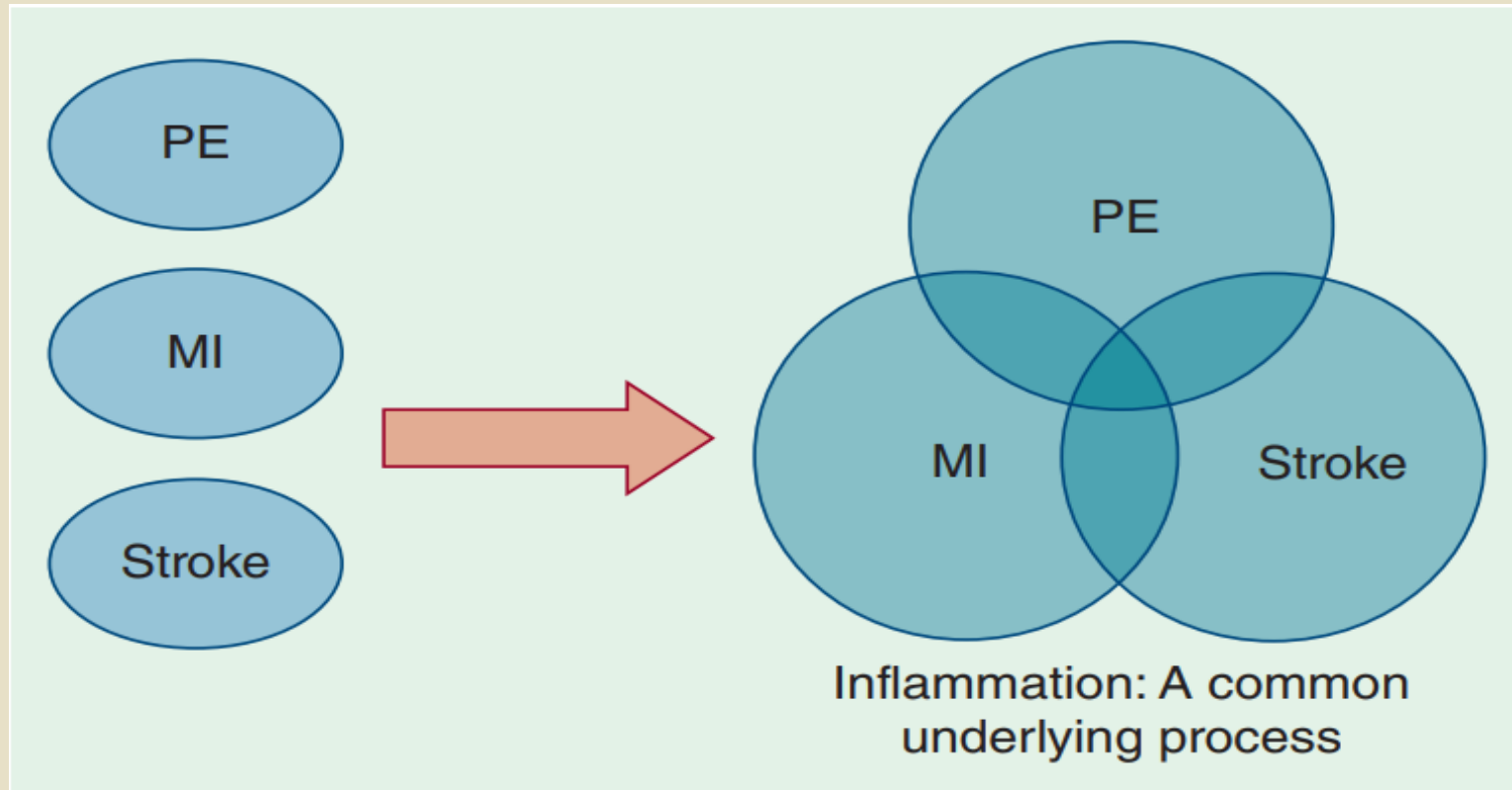
Some risk factors for arterial thrombosis, such as **body mass index and smoking**, were concordant with VTE risk, whereas others, such as blood pressure and triglyceride levels, were discordant

Activated Platelets

Virchow's triad of venous stasis, hypercoagulability, and endothelial injury, usually coupled with an inflammatory trigger, leads to recruitment of activated platelets, which release microparticles. These microparticles contain proinflammatory mediators that bind neutrophils, stimulating them to release their nuclear material and form web-like extracellular networks called *neutrophil extracellular traps*. These prothrombotic networks contain histones that stimulate platelet aggregation and promote platelet-dependent thrombin generation. Venous thrombi form and flourish in this environment of stasis, low oxygen tension, and upregulation of proinflammatory genes

Interaction Between VTE and Atherothrombosis

VTE (**red clot**) and arterial thrombotic (**white clot**) events were previously considered separate entities. However, the presence of carotid artery plaque is associated with double the risk of incident VTE. This observation led to the discovery of a broad interaction of VTE with acute coronary syndrome and with acute ischemic stroke . These three vascular conditions share similar risk factors and similar pathophysiology: inflammation, hypercoagulability, and endothelial injury. Patients who suffer VTE are more than twice as likely to have a future MI or stroke. Conversely, patients with MI or stroke are more than twice as likely to suffer a future VTE.



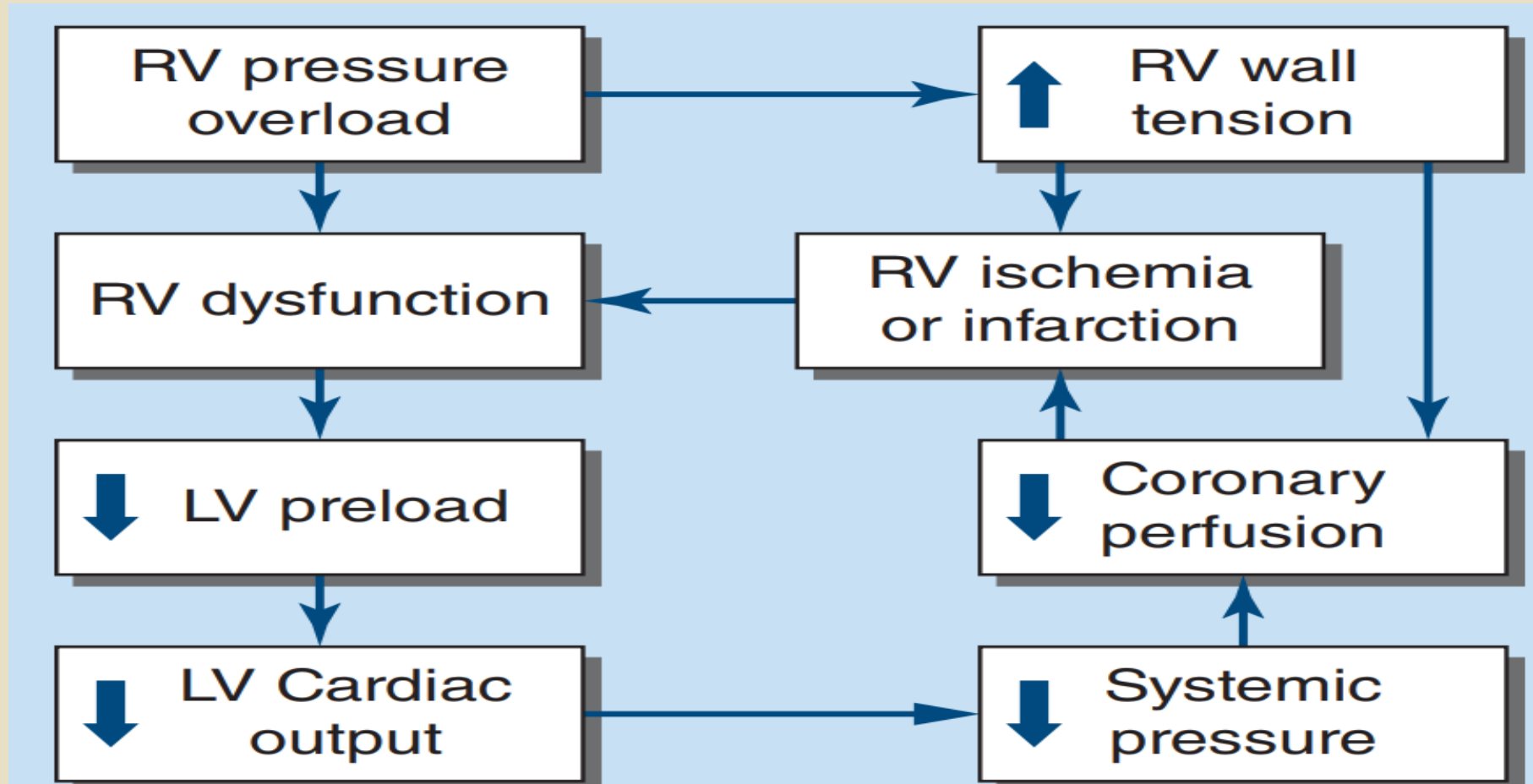
Broad interaction between VTE and atherothrombosis.

Embolization

When DVTs detach from their site of formation, they embolize to the vena cava, right atrium, and right ventricle and lodge in the pulmonary arterial circulation, thereby causing acute PE. Many patients with PE have no evidence of DVT because the leg thrombus has already embolized to the lungs. Paradoxically, these thrombi occasionally embolize to the arterial circulation through a patent foramen ovale or atrial septal defect.

Physiology

The **most common** gas exchange abnormalities are arterial **hypoxemia** and an increased alveolar-arterial O₂ tension gradient, which represent the inefficiency of oxygen transfer across the lungs. Anatomic **dead space increases** because breathed gas does not enter gas exchange units of the lung. Physiologic dead space increases because ventilation to gas exchange units exceeds venous blood flow through the pulmonary capillaries



Pathophysiology of pulmonary embolism

Other pathophysiologic abnormalities include:

1. *Increased pulmonary vascular resistance* due to vascular obstruction or platelet secretion of vasoconstricting neurohumoral agents such as serotonin.
2. *Impaired gas exchange* due to *increased* alveolar dead space from vascular obstruction,
3. *Alveolar hyperventilation* due to reflex stimulation of irritant receptors.
4. *Increased airway resistance* due to constriction of airways distal to the bronchi.
5. *Decreased pulmonary compliance* due to lung edema, lung hemorrhage, or loss of surfactant.

■ CLASSIFICATION OF PTE AND DVT

Pulmonary Embolism

Massive (high-risk) PE accounts for 5–10% of cases and is usually characterized by systemic arterial hypotension and extensive thrombosis affecting at least half of the pulmonary vasculature. Dyspnea, syncope, hypotension, and cyanosis are hallmarks of massive PE. Patients with massive PE may present in cardiogenic shock and can die from multisystem organ failure.

Submassive (intermediaterisk) PE accounts for 20–25% of patients and is characterized by RV dysfunction despite normal systemic arterial pressure. The combination of right heart failure and release of cardiac biomarkers such as troponin indicates a high risk of clinical deterioration.

Low-risk PE constitutes about 65–75% of cases. These patients have an excellent prognosis.

Deep-Venous Thrombosis *Lower extremity DVT* usually begins in the calf and can propagate proximally to the popliteal, femoral, and iliac veins.

Leg DVT is ~10 times more common than *upper extremity DVT*, which is often precipitated by placement of pacemakers, internal cardiac defibrillators, or indwelling central venous catheters. The likelihood of upper extremity DVT increases as the catheter diameter and number of lumens increase.

Superficial venous thrombosis usually presents with erythema, tenderness, and a “palpable cord”; it is most common in the lower extremities because of varicose veins and in the upper extremities because of indwelling intravenous catheters. Superficial veins may be visible in the chest wall (*Urschel’s sign*). Patients are at risk for extension of the superficial vein thrombosis to the deep-venous system

■ DIAGNOSIS

Clinical Evaluation

PTE is known as “the great masquerader.”

Diagnosis is difficult because symptoms and signs are nonspecific.

The most common symptom of PE is unexplained breathlessness. When occult PE occurs concomitantly with overt congestive heart failure or pneumonia, clinical improvement often fails to ensue despite standard medical treatment of the concomitant illness. This scenario provides a clinical clue to the possible coexistence of PE.

With DVT, the most common symptom is a **cramp or “charley horse”** in the lower calf that persists and intensifies over several days.

Wells Point Score criteria

Clinical Pearls

Not all leg pain is due to DVT, and not all dyspnea is due to PTE

Sudden, severe calf discomfort suggests a **ruptured Baker's cyst**. Fever and chills often herald **cellulitis** rather than DVT.

Physical findings, if present, may consist only of mild palpation discomfort in the lower calf. However, massive DVT often presents with marked thigh swelling, tenderness, and erythema. If a leg is diffusely edematous, DVT is unlikely, except for the most serious form of DVT, *phlegmasia cerulea dolens*. **Recurrent left thigh edema**, especially in young women, raises the possibility of **May-Thurner syndrome**, with right proximal iliac artery compression of the left proximal iliac vein. This syndrome may be associated with a DVT. Upper extremity venous thrombosis may present with asymmetry in the supraclavicular fossa or in the circumference of the upper arms.

Pulmonary infarction usually indicates a **small** PE. This condition is exquisitely painful because the thrombus lodges peripherally, near the innervation of pleural nerves.

Nonthrombotic PE etiologies include fat embolism after pelvic or long bone fracture, tumor embolism, bone marrow, and air embolism. Cement embolism and bony fragment embolism can occur after total hip or knee replacement. Intravenous drug users may inject themselves with a wide array of substances that can embolize, such as hair, talc, and cotton. *Amniotic fluid embolism* occurs when fetal membranes leak or tear at the placental margin.

TABLE 290-3 Differential Diagnosis of DVT and PE

DVT

Ruptured Baker's cyst

Muscle strain/injury

Cellulitis

Acute postthrombotic syndrome/venous insufficiency

PE

Pneumonia, asthma, chronic obstructive pulmonary disease

Congestive heart failure

Pericarditis

Pleurisy: "viral syndrome," costochondritis, musculoskeletal discomfort

Rib fracture, pneumothorax

Acute coronary syndrome

Anxiety

Vasovagal syncope

TABLE 290-2 Clinical Decision Rules**Low Clinical Likelihood of DVT if Point Score Is Zero or Less; Moderate Likelihood if Score Is 1 to 2; High Likelihood if Score Is 3 or Greater**

CLINICAL VARIABLE	DVT SCORE
Active cancer	1
Paralysis, paresis, or recent cast	1
Bedridden for >3 days; major surgery <12 weeks	1
Tenderness along distribution of deep veins	1
Entire leg swelling	1
Unilateral calf swelling >3 cm	1
Pitting edema	1
Collateral superficial nonvaricose veins	1
Alternative diagnosis at least as likely as DVT	−2
High Clinical Likelihood of PE if Point Score Exceeds 4	
CLINICAL VARIABLE	PE SCORE
Signs and symptoms of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100/min	1.5
Immobilization >3 days; surgery within 4 weeks	1.5
Prior PE or DVT	1.5
Hemoptysis	1.0
Cancer	1.0

Nonimaging Diagnostic Modalities

□ BLOOD TESTS

□ D-dimer

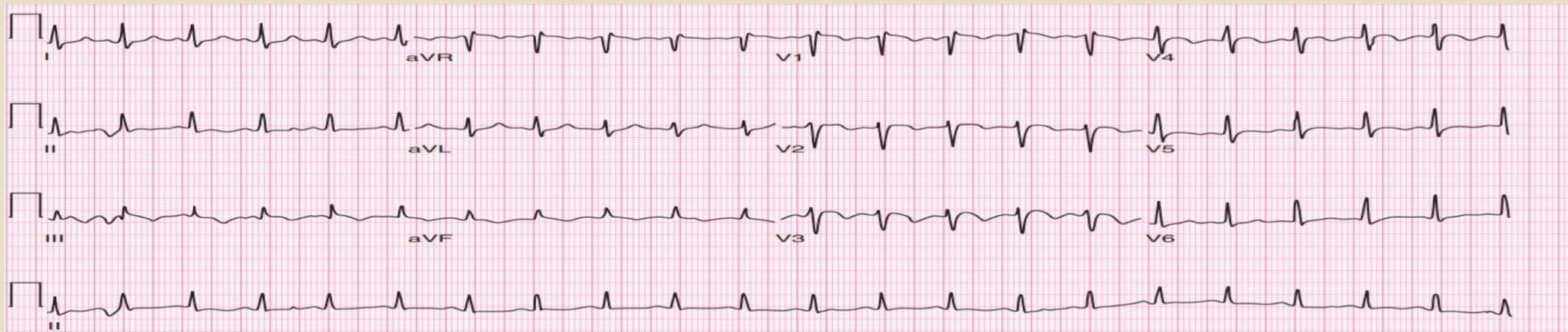
The sensitivity of an abnormally elevated d-dimer is >95% for PE. A normal d-dimer is a useful “rule out” test for PE in patients with low pretest probability. However, the d-dimer assay is not specific. Levels increase in patients with MI, pneumonia, sepsis, cancer, and the postoperative state, and those in the second or third trimester of pregnancy. Therefore, d-dimer testing rarely has a useful role among hospitalized patients because levels are frequently elevated due to systemic illness.

The upper limit of normal for d-dimer was considered to be 500 ng/mL; however, guidelines now recommend use of an ageadjusted d-dimer when ruling out acute PE. The age-adjusted d-dimer applies to patients older than 50 years of age with low or intermediate clinical probability of PE. To calculate the upper limit of normal d-dimer in these patients, multiply the age by 10. For example, a 70-year-old patient suspected of PE would have 700 ng/mL as the upper limit of normal for d-dimer.

ELEVATED CARDIAC BIOMARKERS Serum troponin increases because of RV microinfarction. Myocardial stretch causes release of brain natriuretic peptide or NT-pro-brain natriuretic peptide.

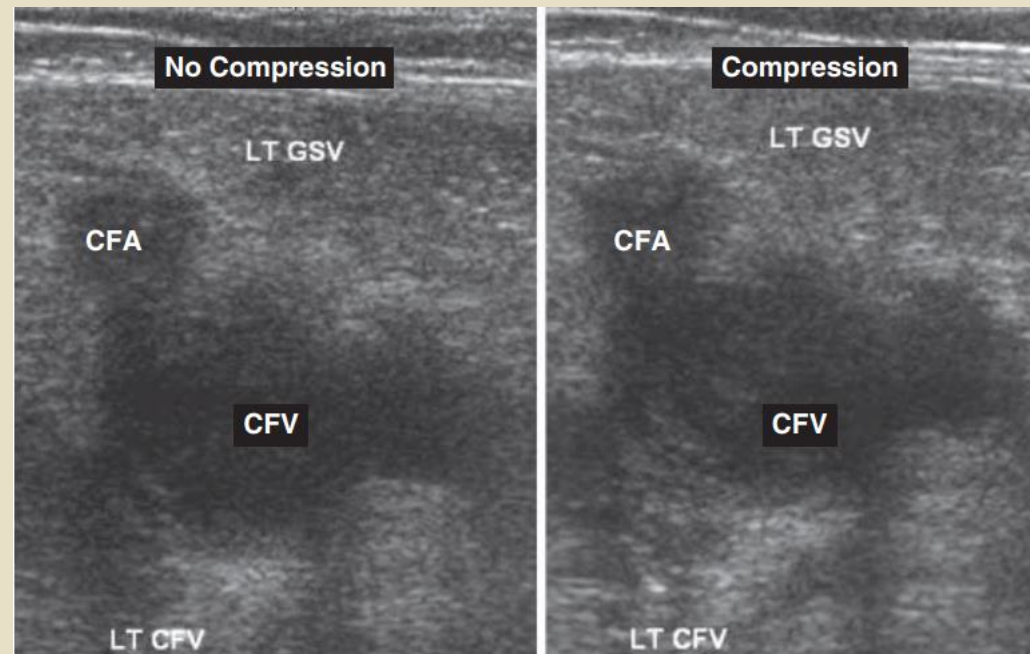
ELECTROCARDIOGRAM The most frequently cited abnormality, in addition to sinus tachycardia, is the S1Q3T3 sign: an S wave in lead I, a Q wave in lead III, and an inverted T wave in lead III .

This finding is relatively specific but insensitive. RV strain and ischemia cause the most common abnormality, T-wave inversion in leads V1 to V4 .



Noninvasive Imaging Modalities

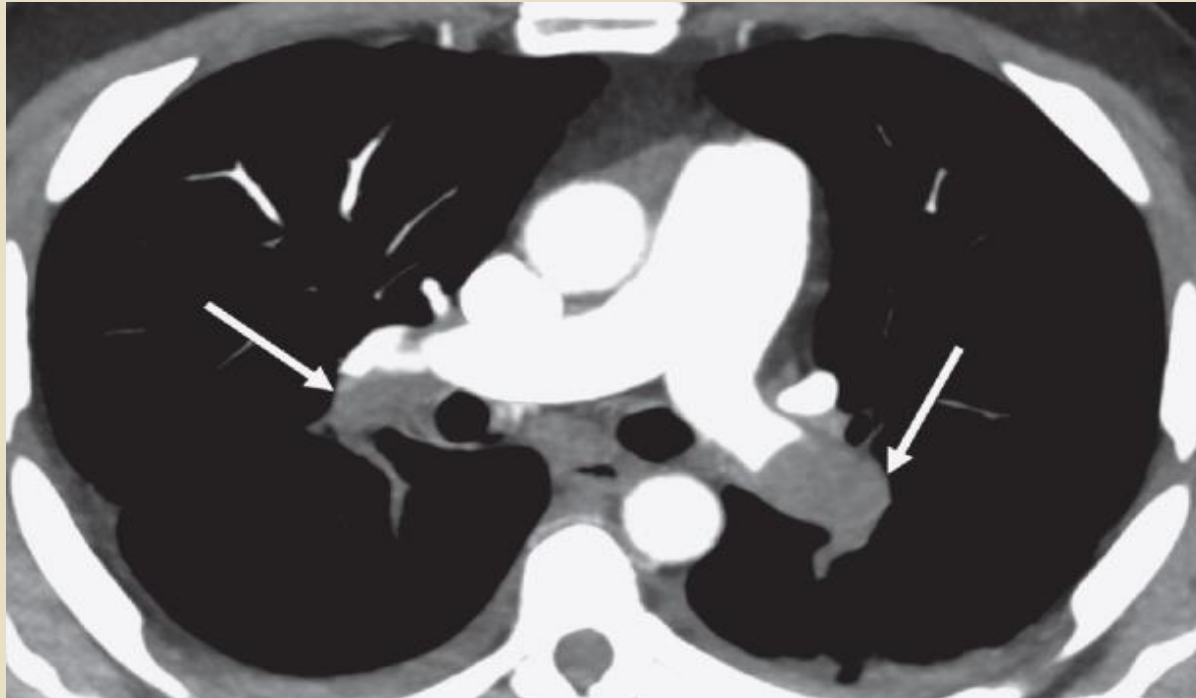
□ **VENOUS ULTRASONOGRAPHY** Ultrasonography of the deep-venous system relies on loss of vein compressibility as the primary diagnostic criterion for DVT. When a normal vein is imaged in cross-section, it readily collapses with gentle manual pressure on the ultrasound transducer.



CHEST ROENTGENOGRAPHY

A normal or nearly normal chest x-ray often occurs in PE. Well-established abnormalities include **focal oligemia** (*Westermarck's sign*), a peripheral triangular-shaped density usually located at the pleural base (*Hampton's hump*—which is usually due to **pulmonary infarction**), and an enlarged right descending pulmonary artery (*Palla's sign*).

CT pulmonary angiography with intravenous contrast is the **principal imaging** test for the diagnosis of PE



LUNG SCANNING

Ventilation/perfusion lung scanning has become a second-line diagnostic test for PE, used mostly for patients who cannot tolerate intravenous contrast.

A **high-probability** scan for PE is defined as **two or more segmental** perfusion defects in the presence of normal ventilation. The diagnosis of PE is very unlikely in patients with normal and nearly normal scans and, in contrast, is ~90% certain in patients with high-probability scans.

MAGNETIC RESONANCE (MR) (CONTRAST-ENHANCED) IMAGING

When pelvic or leg ultrasound is equivocal, MR venography with gadolinium contrast is an excellent imaging modality to diagnose DVT. MR pulmonary angiography may detect large proximal PE but is not reliable for smaller segmental and subsegmental PE.

ECHOCARDIOGRAPHY

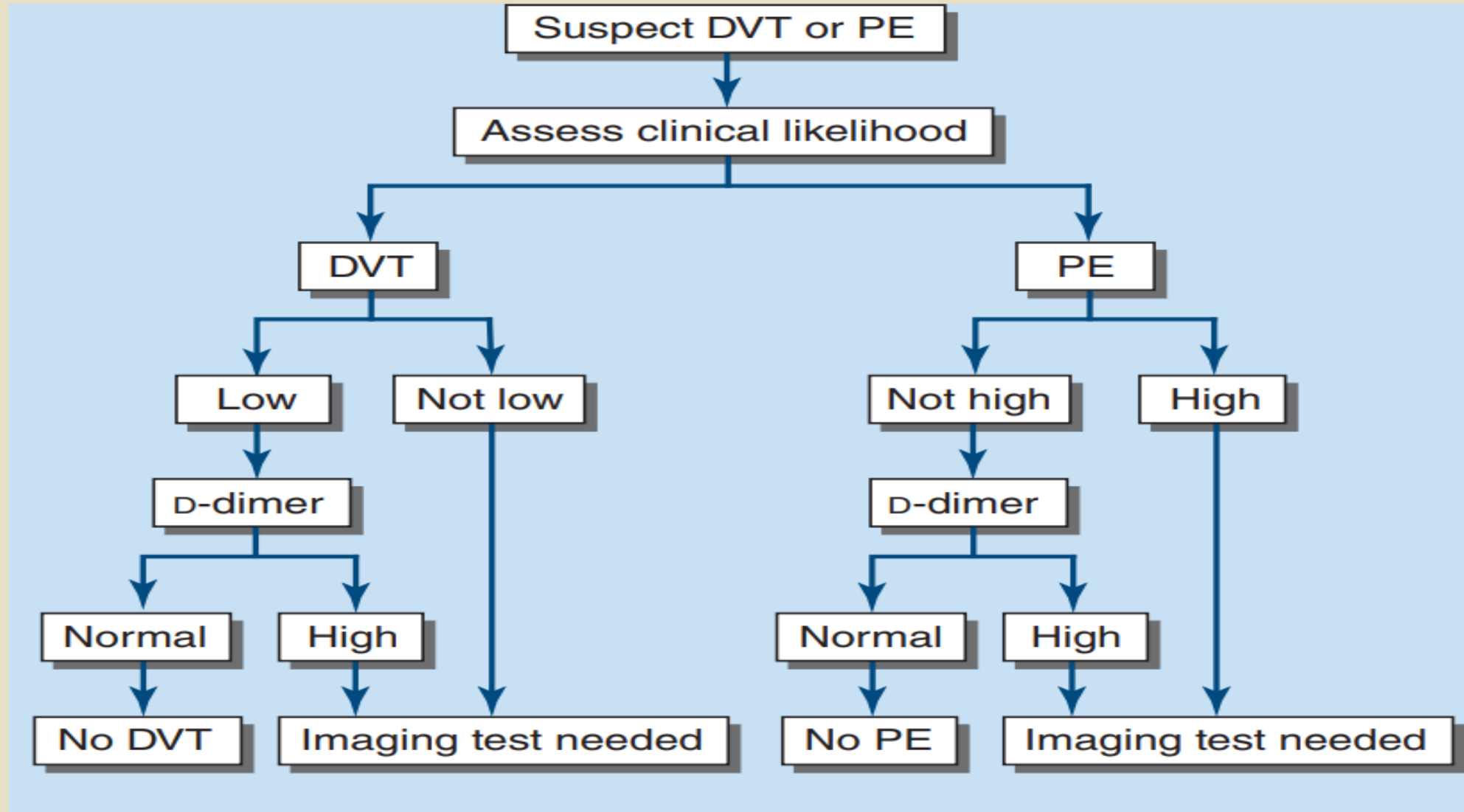
Echocardiography is *not* a reliable diagnostic imaging tool for acute PE because most patients with PE have normal echocardiograms. However, echocardiography is very useful for detecting conditions that may mimic PE, such as acute MI, pericardial tamponade, and aortic dissection. Transthoracic echocardiography rarely images thrombus directly in the main pulmonary artery or the right or left main branches. The best-known indirect sign of PE on transthoracic echocardiography is McConnell's sign: hypokinesis of the RV free wall with normal or hyperkinetic motion of the RV apex

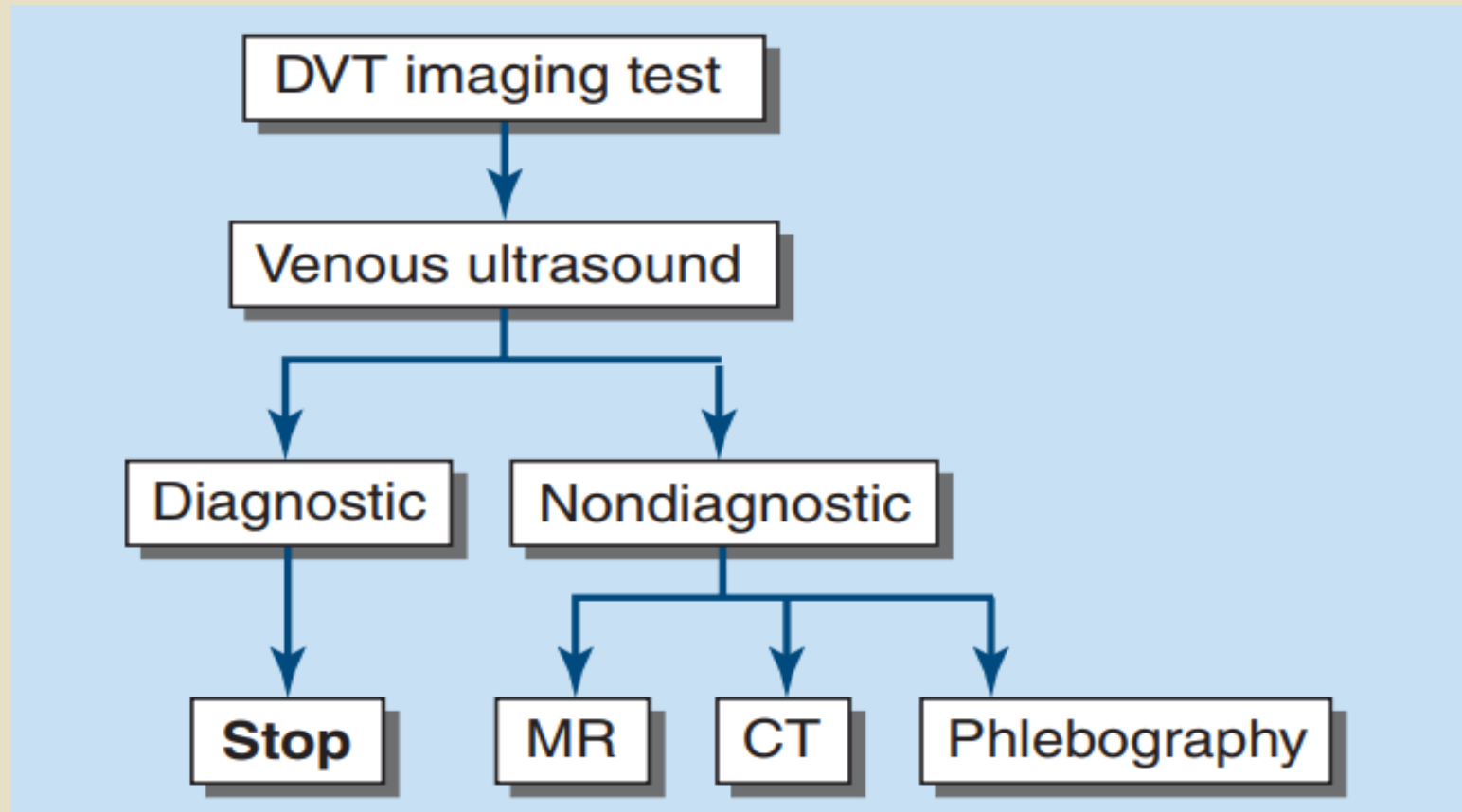
Invasive Diagnostic Modalities

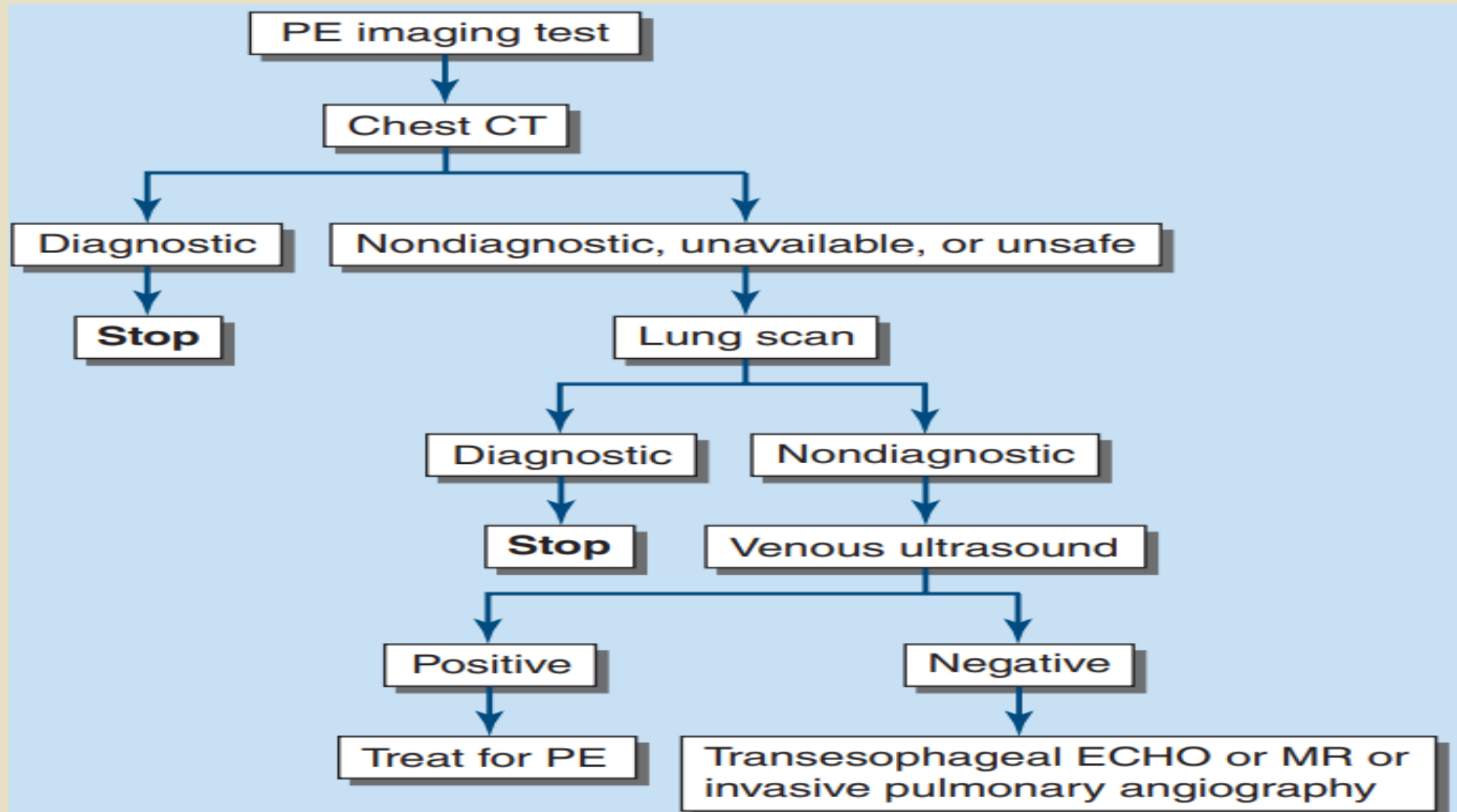
□ **PULMONARY ANGIOGRAPHY** Chest CT pulmonary angiography with contrast (see above) has virtually replaced invasive pulmonary angiography as a diagnostic test. Invasive catheter-based diagnostic testing is reserved for patients with technically unsatisfactory chest CTs and for those in whom an interventional procedure such as catheter-directed thrombolysis or embolectomy is planned. A definitive diagnosis of PE requires visualization of an intraluminal filling defect in more than one projection. Secondary signs of PE include abrupt occlusion (“cut-off”) of vessels, segmental oligemia, avascularity, and a prolonged arterial phase with slow filling and tortuous, tapering peripheral vessels.

CONTRAST PHLEBOGRAPHY Venous ultrasonography has virtually replaced contrast phlebography as the principal diagnostic test for suspected DVT. However, contrast phlebography is used when an interventional procedure is planned.

Integrated Diagnostic Approach An integrated diagnostic approach streamlines the workup of suspected DVT and PE







TREATMENT

Deep-Venous Thrombosis

UPPER EXTREMITY DVT

ISOLATED CALF DVT

Almost all isolated calf DVT patients received anticoagulation, and nearly half were anticoagulated for at least 1 year.

FIBRINOLYSIS

ANTICOAGULATION

COMPRESSION STOCKINGS

ANTICOAGULATION

There are three major strategies for anticoagulation:

- 1) the well-established—but waning—strategy of parenteral anticoagulation with unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or fondaparinux either as monotherapy or more often “bridged” to warfarin;
- (2) parenteral anticoagulation, switched after 5 days to dabigatran (a direct thrombin inhibitor) or edoxaban (an anti-Xa agent); or
- (3) oral anticoagulation monotherapy with rivaroxaban or apixaban (both anti-Xa agents) with a 3-week or 1-week loading dose, respectively.

For patients with VTE in the setting of suspected or proven heparin-induced thrombocytopenia, one can choose between two intravenous direct thrombin inhibitors: argatroban (metabolized by the liver) or bivalirudin (metabolized by the kidney), or subcutaneously administered fondaparinux

TREATMENT

Pulmonary Embolism

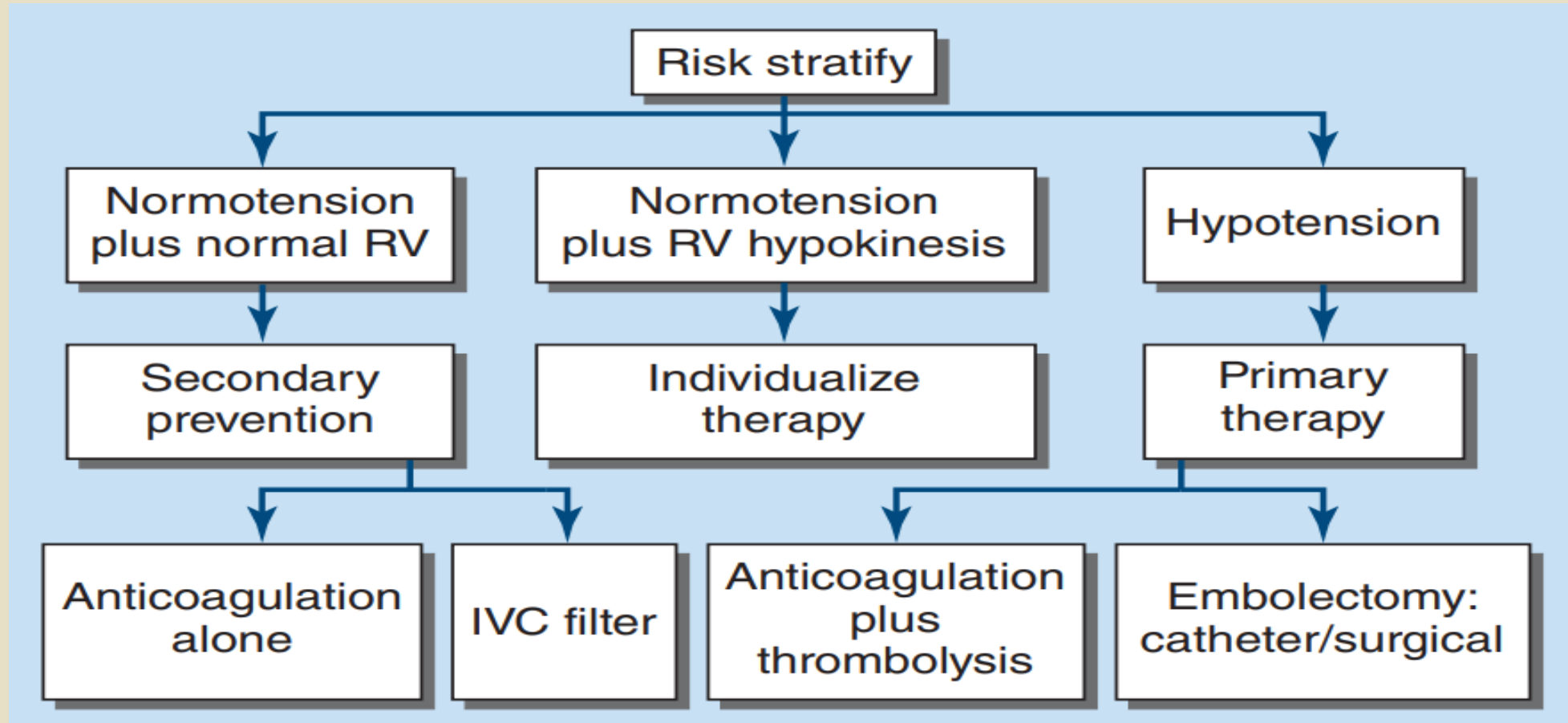


TABLE 290-5 Take-Home Points from the European Society of Cardiology 2019 Pulmonary Embolism Guidelines

1. Terminology such as “provoked” versus “unprovoked” PE/DVT is no longer supported by the guidelines, as it is potentially misleading and not helpful for decision-making regarding the duration of anticoagulation.
2. Extended oral anticoagulation without an end date should be considered for patients with a first episode of PE and:
 - a. No identifiable risk factor
 - b. A persistent risk factor
 - c. A minor transient or reversible risk factor

INFERIOR VENA CAVA FILTERS

The two principal indications for insertion of an inferior vena cava filter are (

- 1) active bleeding that precludes anticoagulation and
- (2) recurrent venous thrombosis despite intensive anticoagulation.

Prevention of PE in patients who are not candidates for anticoagulation is a much “softer” indication for filter placement. The filter itself may fail by permitting the passage of small- to medium-size clots via collateral veins that develop. Paradoxically, by providing a nidus for clot formation, filters may increase the DVT rate even though they usually prevent PE. In most situations, place a retrievable rather than a permanent filter

TABLE 290-6 Risk of Recurrent Venous Thromboembolism After Discontinuing Anticoagulation (European Society of Cardiology 2019 Pulmonary Embolism Guidelines)

RISK OF RECURRENCE	EXAMPLES
Low risk (<3% per year)	Major surgery or trauma
Intermediate risk (3–8% per year)	Minor surgery Hospitalized with acute medical illness Pregnancy/estrogens Long-haul flight Inflammatory bowel disease Autoimmune disease No identifiable risk factor (formerly called “unprovoked”)
High risk (>8% per year)	Active cancer Antiphospholipid syndrome

TABLE 290-7 Prevention of Venous Thromboembolism Among Hospitalized Patients

CONDITION	PROPHYLAXIS STRATEGY
High-risk nonorthopedic surgery	Unfractionated heparin 5000 units SC bid or tid Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily
Medical oncology (ambulatory)	Apixaban or rivaroxaban for up to 6 months in high-risk patients with cancer starting a new chemotherapy regimen
Cancer surgery, including gynecologic cancer surgery	Enoxaparin 40 mg daily, consider 1 month of prophylaxis
Major orthopedic surgery	Aspirin 81 mg twice daily Rivaroxaban 10 mg daily, beginning 6–10 h postoperatively Dabigatran 110 mg first day, then 220 mg daily Apixaban 2.5 mg bid, beginning 12–24 h postoperatively Warfarin (target INR 2.0) Enoxaparin 40 mg daily Dalteparin 2500 or 5000 units daily Fondaparinux 2.5 mg daily

Medically ill patients, especially if immobilized, with a history of prior VTE, with an indwelling central venous catheter, or with cancer (but without active gastroduodenal ulcer, major bleeding within 3 months, or platelet count <50,000)

Medically ill patients about to be discharged from hospital

Anticoagulation contraindicated

Unfractionated heparin 5000 units bid or tid
Enoxaparin 40 mg daily
Dalteparin 2500 or 5000 units daily
Fondaparinux 2.5 mg daily

Rivaroxaban 10 mg daily for about 5 weeks (rarely prescribed for this indication)

Intermittent pneumatic compression devices and/or graduated vascular below-knee compression stockings

Abbreviations: INR, international normalized ratio; VTE, venous thromboembolism.

Thanks for Your Attention

