VENOUS THROMBOEMBOLISM

Relevant Guidelines

ESC 2019 guidelines on pulmonary embolism

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2019.

AHA/ACC 2026 Guideline on pulmonary embolism

2026 AHA/ACC/ACCP/ACEP/CHEST/SCAI/SHM/SIR/SVM/SVN Guideline for the Evaluation and Management of Acute Pulmonary Embolism in Adults. *Circulation*. 2026;153:e977-e1051.

ASH 2020 guidelines on DVT

Venous Thromboembolism Clinical Practice Guidelines (ASH, 2020). *Hematology*. 2020.

ESC 2022 Guidelines on cardio-oncology

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022.

ESC 2026 GL on chronic kidney disease

2026 ESC Guidelines for the management of cardiovascular disease and chronic kidney disease, in collaboration with the European Renal Association (ERA). *Eur Heart J*. 2026.

ESC 2025 guidelines on pregnancy

2025 ESC Guidelines for the management of cardiovascular diseases and pregnancy. *Eur Heart J*. 2025.

Relevant Scientific Statements and Position Papers

AHA 2011 scientific statement on pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension.

Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123:1788-830.

AHA 2020 Statement on VTE Research

Venous Thromboembolism Research Priorities. A Scientific Statement From the American Heart Association and the International Society on Thrombosis and Haemostasis. *Circulation*. 2020;142: e85-e94.

AHA 2020 Statement on Pregnancy

Cardiovascular Considerations in Caring for Pregnant Patients: A Scientific Statement From the American Heart Association. *Circulation*. 2020;141:e884-e903.

AHA 2025 Scientific Statement on Postthrombotic Syndrome

Revisiting the Open Vein Hypothesis to Reduce the Postthrombotic Syndrome: Implications for Multidisciplinary Care and Research: A Scientific Statement From the American Heart Association. Circulation. 2025.

ACC 2026 Report on Anticoagulation

Direct Oral Anticoagulants in Primary and Secondary Prevention of Thrombotic Events: 2026 ACC Scientific Statement: A Report of the American College of Cardiology. *J Am Coll Cardiol*. 2026.

VENOUS THROMBOEMBOLISM: EPIDEMIOLOGY AND AETIOLOGY

Definitions

Venous thromboembolism (VTE) denotes pulmonary embolism (PE) and deep venous thrombosis (DVT),[1] although whether these two conditions belong to the same disease entity is disputable.[2] Pulmonary embolism (PE) refers to embolization of, usually, thrombotic material to pulmonary arteries with complete or partial occlusion of one or more of their branches.

Epidemiology

The annual incidence of VTE is approximately 1-2 case per 1000 person-years, whereas that of PE is 0.5-1. [1, 3] The risk of a first venous thrombosis is twice as high in men as in women who are not exposed to the reproductive risk factors of oral contraception use, pregnancy/puerperium, and postmenopausal hormone therapy.[4] Blacks have a 3-fold higher incidence for PE than whites, and blacks and Hispanics suffer fatal PE at a significantly younger age than whites,[5] but this finding has not been confirmed in all epidemiological studies.[6] VTE confers an increased risk of death.[7] The 30-day mortality risk for VTE patients was recently estimated 3% for DVT and 31% for PE versus 0.4% for a comparison cohort.[8]

Aetiology

Venous stasis, hypercoagulability, and endothelial damage predispose to VTE (Table 1). The pathogenesis of VTE after surgery is incompletely understood. Tissue factor exposed at the surgical site is thought to be the major driver through the extrinsic pathway of coagulation. Recent observations on the role of factor XI, indicate that the intrinsic pathway is also essential. [9] Strong provoking risk factors for venous thromboembolism include major ***surgery*** (especially orthopaedic) and active ***cancer***, but most events are unprovoked (Figure 1).[10, 11] Orthopedic surgery, in particular, is an established predisposing factor, and patients with cancer have a substantially increased risk of both arterial and venous thromboembolism.[12-14] However, among patients with a first unprovoked venous thromboembolism the prevalence of occult cancer is low. Routine screening with CT of the abdomen and pelvis do not provide any benefit.[15] ***Pregnancy*** is an established predisposing factor. High endogenous concentrations of estradiol and testosterone in women and men in the general population are not associated with increased risk of VTE, DVT or PE. [16] However, the Women's Health Initiative study documented a 2-fold increase of VTE among postmenopausal women on

combined oral estrogen and progesterone preparations,[17] and a history of PE or DVT is an absolute contraindication to ***oral contraceptives*** and ***hormone-replacement therapy***. Combined oral contraceptives with levonorgestrel or norgestimate confer half the risk of venous thrombosis than oral contraceptives containing desogestrel, gestodene, or drospirenone, and progestin only pills do not confer an increased risk of venous thrombosis.[18, 19] Except for injection of medroxyprogesterone acetate, progestin-only contraception seems to be the least thrombogenic hormonal contraception for women carrying genetic hemostatic variations.[20] Conjugated equine oral estrogens are associated with a higher risk of incident venous thrombosis and possibly myocardial infarction than oral estradiol in menopausal women.[21] The route of administration is also important. In menopausal women, transdermal estrogen combined with progesterone appears to be the safest option.[22] Regarding contraception, according to large Danish registries of women 25-49 year-old, free of VTE, combined contraceptive transdermal patches and vaginal rings result in an increased risk of venous thrombosis. The risk is not significantly increased with use of subcutaneous implants or the levonorgestrel intrauterine system.[18] ***Obesity, smoking,*** and ***long-haul air travel*** are also recognized causes of PE. Thrombosis of the popliteal vein or more proximally, and especially iliofemoral deep vein thrombosis, carries a higher risk for PE than isolated calf vein thrombosis.[23] ***Heart diseases*** increase the near-term risk for pulmonary embolism not associated with diagnosed peripheral vein thrombosis.[24] VTE risk in heart failure is 1.5-2.9 higher than in patients without heart failure,[25] and a high NT-proBNP plasma concentration, is a useful index of high short-term risk of VTE.[26] ***Traditional cardiovascular risk factors*** have not been found independent risk factors for venous thromboembolism.[27] However, ***older age, smoking,*** and ***adiposity*** are consistently associated with higher VTE risk.[28] Higher ***systolic blood pressure*** has an inverse association with VTE risk, which may be caused by competing risk of comorbid conditions such as atrial fibrillation, which is strongly associated with high blood pressure, with subsequent anticoagulant drug use being protective against VTE.[27] There is an increased risk for VTE in patients with ***rheumatoid arthritis***, ***psoriasis*** and ***psoriatic arthritis***.[29] Sickle cell disease is also a recognized cause of VTE.[30] ***Acute infection*** that requires hospitalization, blood transfusion and the use of erythropoiesis stimulating agents are also possible triggers for acute VTE in noncancer patients.[31] Coronavirus disease (***COVID-19***) predisposes patients to arterial and venous thrombosis and PE.[32-34] Peripherally inserted ***central catheters*** are associated with an increased risk of venous thromboembolism compared to central venous catheters, particularly in the critically ill or patients with a malignancy.[35] ***IVC anomalies*** are a rare cause of DVT in the young.[15, 36] In 30% of cases PE occurs unprovoked, in the absence of any predisposing factors.[3] ***Thrombophilias*** are inherited and acquired hypercoagulable states that increase the risk of venous and, in some cases, arterial thrombosis. (Tables 2 and 3).[37] [38] The most common

inherited thrombophilias are factor V Leiden (autosomal dominant single point mutation that brings resistance to activated protein C that actually predisposes to DVT rather than PE per se [2]), and a mutation in the prothrombin gene (G20210A). Factor V Leiden increases the frequency of VTE at any age, but mainly in those >=70 year-old.[38] It is not associated with increased risk of atherothrombotic events and mortality in patients with established and treated CHD.[39] A family history of thromboembolism in >= 2 siblings is a major risk factor for venous thromboembolism.[40] However, it should be noted that inherited thrombophilias do not contribute to arterial thrombosis. In addition, the risk of recurrence in patients with unprovoked VTE is not influenced by factor V Leiden and the prothrombin gene mutation, whereas it is increased by 40% in patients with a lupus anticoagulant.[41] There is no evidence that patients with VTE and inherited thrombophilia should be treated differently than those with VTE and without thrombophilia.[41]

Antiphospholipid syndrome is an autoimmune disease characterized by venous thromboembolism, arterial thrombosis, and obstetric morbidities in the setting of persistently positive levels of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibody, and anti–β-2 glycoprotein-1 antibodies) measured on 2 different occasions 12 weeks apart.[42, 43] The diagnosis is established if at least one clinical and one laboratory criterion are met, although some uncertainty exists.[43]. Having a lupus anticoagulant present confers an odds ratio of 11 for thrombosis compared with control subjects versus 1.6 in the presence of anticardiolipin antibodies alone. Patients who are positive for lupus anticoagulant, anticardiolipin antibody, and anti–β-2 glycoprotein-1 antibodies (so-called triple-positive patients) are at particularly high risk for rethrombosis.[44]

Diagnostic thrombophilia testing

Thrombophilia is detected in approximately 30% of patients with symptomatic VTE.[38] Most persons with a thrombophilia do not develop thrombosis, and there are no absolute indications for thrombophilia testing.[45] In patients with pulmonary embolism, it is probably cost-effective in men<70 years of age and women <50 years of age.[38]

In case of young patients with **VTE** in the absence of other predisposing factors, the laboratory evaluation should be selective and individualized, and may include: ***Blood cell count with peripheral smear, liver and renal function, and serum protein electrophoresis.*** Genetic testing for ***factor V Leiden*** and ***prothrombin*** mutations, if an inherited thrombophilia is suspected, and testing for ***antiphospholipid antibodies*** (eg, lupus anticoagulant, anticardiolipin antibodies, anti–β_2-glycoprotein-1 antibodies). Testing for antiphospholipid antibodies require confirmation 12 weeks after an initial positive result.

Patients who develop **arterial thrombosis**, in particular, should be considered for testing for ***antiphospholipid antibodies***, ***heparin-induced thrombocytopenia, myeloproliferative disorders, and vasculitis.*** Acute thrombosis can transiently reduce the levels of antithrombin and, occasionally, proteins C and S, which are acute-phase reactants. Testing, therefore, is recommended at least 6 weeks after the acute phase of thrombosis or childbirth. Heparin therapy can lower antithrombin activity and antigen levels and can impair the interpretation of clot-based assays for a lupus anticoagulant. A delay of more than 1 day after cessation of heparin is necessary before testing is usually feasible. Warfarin therapy reduces the activity and antigen levels of the vitamin K–dependent factors and should be stopped for at least 2 weeks before testing. It is more effective than NOACs in preventing arterial thrombosis (without any difference in VTE) in patients with antiphospholipid syndrome.[46] Novel oral anticoagulants may cause false-positive lupus anticoagulant (dilute Russell viper venom time) testing and falsely low antithrombin activity, and should be stopped at least 2-3 days. Direct leukocyte genomic DNA testing for factor V Leiden and prothrombin G20210A mutations is unaffected by anticoagulation therapy; such testing can be performed at any time.[45]

In a recent meta-analysis, both hereditary and acquired thrombophilia are associated with an increased risk of recurrent VTE after discontinuation of anticoagulation. The strongest associations were observed with antiphospholipid antibody syndrome and certain high-risk inherited thrombophilias, whereas heterozygous factor V Leiden and G20210A mutations were associated with more modest increases in risk. Evidence for protein C and protein S deficiencies was inconclusive.[47] Thus, thrombophilia can help refine recurrence-risk assessment, but the decision to stop or continue anticoagulation should be individualized rather than based on thrombophilia status alone.

Prophylaxis and Therapy of VTE in Patients with Cancer

Thromboembolic events that develop during cancer and chemotherapy include both venous and arterial thromboembolism. Cancer-associated thrombosis is determined by the prothrombotic milieu induced by cancer, the prothrombotic properties of certain anticancer and adjunctive therapies, and patient-related risk factors. VTE, including deep vein thrombosis (DVT) and PE, is the second-leading cause of death in patients with malignancies.[11] Recommendations for the management of these patients are presented in Figure 2 and Tables 4 and 5 (see also Cardio-oncology).

Cancer should be suspected in patients who have recurrent idiopathic VTE,[48] but routine screening with CT of the abdomen and pelvis is not indicated.[15] Female sex, lung cancer, stage TNM stage >1, solid tumors subjected to chemotherapy, and previous VTE

indicate a higher risk of VTE in cancer patients.[49]

Prophylaxis of VTE in Orthopaedic Surgery

The risk of venous thromboembolism after major orthopaedic surgery, and especially total hip or knee replacement or hip-fracture surgery that result in transient reduced mobility is high and anticoagulant thromboprophylaxis is recommended until mobilization. The need for thromboprophylaxis after non-major orthopaedic surgery is controversial and not deemed necessary in the USA[50] but indicated in Europe in patients with additional risk factors.[51] Rivaroxaban (10 mg od) has been found more effective than enoxaparin (40 mg SC) in the prevention of venous thromboembolic events during a period of immobilization after nonmajor orthopedic surgery of the lower limbs (PRONOMOS trial).[52]

Pregnancy

The incidence of pregnancy-related VTE (including post-partum) is 1.2 per 1000 deliveries, and it is a major cause of pregnancy-related morbidity and mortality. Pregnancy-related VTE has a fatality rate of 0.68% and a recurrence rate (during pregnancy and post-partum) of 4.27%, which is higher postpartum.[53] Recommendatiosn are provided in Tables 6 and 7.

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