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# Epidemiology, Pathophysiology, Stratification, and Natural History of Pulmonary Embolism

Nicholas J. Giordano, MA,* Paul S. Jansson, MD, MS,†,‡,§ Michael N. Young, MD,‖ Kaitlin A. Hagan, ScD, MPH,¶ and Christopher Kabrhel, MD, MPH*,¶

**Pulmonary embolism (PE) is a common and potentially fatal form of venous thromboembolism that can be challenging to diagnose and manage. PE occurs when there is obstruction of the pulmonary vasculature and is a common cause of morbidity and mortality in the United States. A combination of acquired and inherited factors may contribute to the development of this disease and should be considered, since they have implications for both susceptibility to PE and treatment. Patients with suspected PE should be evaluated efficiently to diagnose and administer therapy as soon as possible, but the presentation of PE is variable and nonspecific so diagnosis is challenging. PE can range from small, asymptomatic blood clots to large emboli that can occlude the pulmonary arteries causing sudden cardiovascular collapse and death. Thus, risk stratification is critical to both the prognosis and management of acute PE. In this review, we discuss the epidemiology, risk factors, pathophysiology, and natural history of PE and deep vein thrombosis.**
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**KEYWORDS** PE, DVT, Natural History, VTE

## Introduction

Pulmonary embolism (PE) is a life-threatening manifestation of venous thromboembolism (VTE) that can be challenging to diagnose and manage. VTE is a spectrum of disease that encompasses both PE and deep vein thrombosis (DVT). In DVT, a blood clot forms in the deep veins of the extremities, most commonly in the leg. PE occurs when a portion of the clot from a DVT breaks off, travels through the right heart, and eventually lodges in the pulmonary vasculature. More than 50% of patients with DVT in the lower extremity proximal veins (iliac, femoral, and popliteal) present with a concurrent PE.[1-3] Although the vast majority of patients with VTE survive, VTE can be fatal. The clinical presentation and severity of both PE and DVT is variable, ranging from the minimally symptomatic to cardiopulmonary arrest requiring immediate intervention. In this review, we discuss the epidemiology, risk factors, pathophysiology, and natural history of PE and DVT.

## Epidemiology

VTE is a common disorder. In the United States, as many as 2 million people are diagnosed with DVT every year and 500,000-600,000 have PE.[4] The estimated incidence of PE is 100-200 cases per 100,000 people.[5-8] Males are slightly more likely to develop a VTE than females with an estimated incidence rate of 56 males and 48 females per 100,000 people.[9-11] In recent years, as the population of the United States has grown older and the technology used to diagnose PE has become more accessible and sensitive, multiple studies have reported a rising incidence of PE.[5-8]

*Department of Emergency Medicine, Center for Vascular Emergencies, Massachusetts General Hospital, Boston, MA.
†Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA.
‡Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA.
§Department of Emergency Medicine, Harvard Medical School, Boston, MA.
‖Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA.
¶Channing Division of Network Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA.
Address reprint requests to Nicholas J. Giordano, MA, Department of Emergency Medicine, Center for Vascular Emergencies, Massachusetts General Hospital, Boston, MA. E-mail: ngiordano@mgh.harvard.edu

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Currently, PE is estimated to be responsible for 100,000 annual deaths in the United States and VTE remains the third most common cause of cardiovascular death in the United States.[9,12,13]

There are multiple risk factors that may increase the likelihood of developing VTE (Fig. 1). Risk factors can be divided into 2 main categories: inherited and acquired. Acquired risk factors can be further subdivided into provoking or nonprovoking. The nature of provoking risk factors is that, while present, they increase the risk of PE during a finite time period, after which the risk returns to baseline. In contrast, with nonprovoking risk factors the VTE risk remains elevated over time. The distinction between provoking and nonprovoking factors is important, as this may inform the long-term management strategy such as duration of oral anticoagulation, although the distinction between provoking and nonprovoking is often unclear.

# Risk Factors

## Inherited Risk Factors

Several genetic risk factors are known to increase VTE risk and typically involve disorders in clotting factor production or activity. These include, but are not limited to: factor V Leiden, prothrombin gene mutation (20210-A), antithrombin deficiency, protein C deficiency, protein S deficiency, and hyperhomocysteinemia. Approximately 20-30 single nucleotide polymorphisms have been associated with VTE risk through candidate gene or high-throughput genotyping methods, although for some mutations, the clinical relevance and underlying pathophysiological mechanism remain unclear.[14] Among the most common are factor V Leiden and the prothrombin gene mutation, with estimated prevalences of 4%-5% and 2%-4%, respectively.[15,16] Individuals homozygous for Factor V Leiden are even more predisposed to VTE with a nearly 40-fold increase in risk compared to a 2 to 7-fold increase in heterozygous individuals.[17]

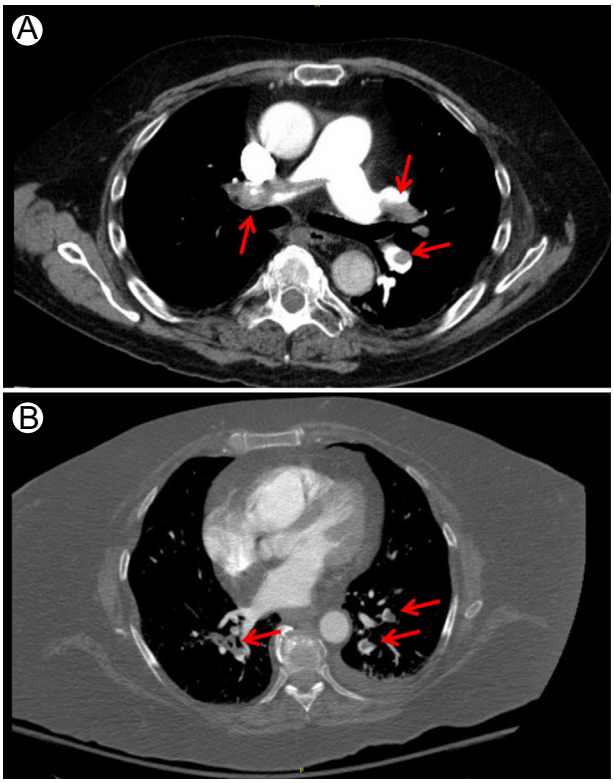


**Figure 1** The combination of acquired and inherited risk factors can lead to a pulmonary embolism. It is important to recognize that some acquired risk factors blur the line between provoked and nonprovoked factors and can be classified as either. Additionally, when provoking and nonprovoking risk factors are combined they result in an increased risk of VTE that is higher than either individual component factor. (Color version of the figure available online.)

Acquired Risk Factors

Acquired risk factors include lifestyle factors, comorbid illnesses, and medical procedures. Some of these factors provoke VTE acutely (provoking factors), while others increase an individual's lifetime risk of developing VTE (nonprovoking factors). It is important to recognize that any attempt to characterize acquired risk factors will be imperfect and can blur the line between provoked and unprovoked. Common provoking factors include surgery, active cancer, immobilization, pregnancy, initiation of hormone therapy, and indwelling vascular catheters. Common nonprovoking factors include: advanced age, venous insufficiency, obesity, rheumatologic conditions, antiphospholipid antibody syndrome, cardiovascular disease, smoking, and previous VTE. Additionally, when provoking factors are combined with nonprovoking risk factors, the resulting increased risk of VTE is higher than each component factor alone.[18]

Provoking Acquired Risk Factors

### Surgery and Trauma

VTE risk increases acutely following surgery. Specifically, patients undergoing orthopedic or oncologic surgery have a particularly high risk for VTE following the procedure.[19] Surgery can result in direct venous injury, immobilization, and inflammation. Local tissue and vessel trauma also occur in patients with severe burns or upper or lower extremity trauma. Secondary tissue damage from surgery or trauma may lead to the release of inflammatory cytokines, which impair fibrinolysis and down regulate endogenous anticoagulants all of which contribute to an increased risk for VTE.

### Cancer

Active cancer is a major risk factor for VTE. Patients with cancer have twice the incidence of DVT and PE compared to patients without cancer. The highest incidence of VTE is observed during the first year after cancer diagnosis and shortly after initiation of treatment.[20] The highest rate of VTE, 4.1%, occurs in the setting of adenocarcinomas.[21] Thus, VTE should remain high on the differential in cancer patients presenting with symptoms or signs suggestive of thrombosis. While active malignancy is a major risk factor