

CHAPTER 2 RISK FACTORS FOR VENOUS THROMBOSIS

**Original authors: Peter K. Henke, Mark H. Meissner
and Thomas W. Wakefield
Abstracted by Kellie R. Brown**

Introduction

Deep vein thrombosis (DVT), blood clots forming in the deep veins often of the leg, pelvic or abdomen but can also occur in the arm veins) is a serious healthcare problem in the US, with over 250,000 patients affected each year and at least 200,000 diagnosed with **pulmonary embolus (PE)**. As our population ages, **DVT** is becoming more common. Among patients with **DVT**, one third of them are diagnosed due to a blood clot traveling in the blood vessels to the lung, causing shortness of breath and chest pain. This is called a **pulmonary embolus (PE)**. The long-term effects of **DVT**, called **post-thrombotic syndrome (PTS)**, affects about 500,000 patients with skin ulcers and millions more with discoloration and other skin changes in the legs. Because of the clot's ability to travel to the lungs, the effects of **post-thrombotic syndrome**, and the risk of recurrent **DVT**, it is important to prevent **DVT** from ever forming (prevention). In order to prevent **DVT** and **PE** some knowledge of who is at risk is needed. This chapter will discuss the common risk factors (those things that increase the blood's tendency to clot) for **DVT**, the changes that occur in a vein after a clot has formed, and what happens to the clot over time.

How common are DVT and PE?

Because many **DVTs** don't cause symptoms, knowing the true incidence is difficult. However, most sources believe that first time, symptomatic **DVT** or **PE** (those patient's who have symptoms from the clotting) in the USA happens in between 71 and 117 cases per 100,000 people. There are approximately 275,000 new **VTE** cases per year in the US, a figure that has not changed in the past 10 years. **VTE** stands for venous thromboembolism, which includes both **DVT** and **PE**.

What causes DVT and PE (VTE)?

There are many causes of **VTE**, including genetic risk factors and environmental risk factors. Some risk factors are permanent, and some, like major surgery, are temporary. Most risk factors have to do with a change in the blood's clotting ability, either due to different factors in the blood, or a change in a patient's activity level. Well established risk factors for **DVT** are discussed below. The development of **DVT** or **PE** most often occurs when a person has more than one risk factor.

What are the risk factors for VTE?

- **Age, Gender and Race**

Age, gender, and race may potentially influence the risk of **VTE**. Among these, age has most consistently been associated with increased **VTE** risk. As **age** increases, so does the risk. This increase in risk appears to be related to several age related factors, including decreased mobility, an increased number of other major risk factors such as cancer, age related changes in the blood's tendency to clot, and changes in the veins themselves.

Gender differences are less clear, with the existing studies differing on whether gender influences risk or not. The lack of consistent data makes it unlikely that there are major gender differences in the incidence of **DVT**. However, the risk in women is higher during childbearing years, whereas between the ages of 45 and 60 the risk may be higher in men.

Race has a variable affect on incidence of thromboembolism. There is evidence to suggest that the occurrence of post-operative **DVT** is less in Asian, Arab, Hispanic, and African populations than among those of European descent. This difference is probably due to genetic factors associated with **VTE**.

- **Surgery**

The increased risk of **DVT** or **PE** associated with surgery is due to decreased ability to move after surgery, and changes in the levels of certain clotting factors in the blood that occur after major surgery. The degree of risk also varies with the age of the patient, the length of the operation, the type of operation, and the presence of other **DVT** risk factors. Without treatment, **DVT** can occur in about 25% of patients undergoing general surgery, and can be up to 50% in patients undergoing hip or knee surgery. This risk can be greatly decreased with the appropriate use of sequential compression devices on the legs and/or doses of blood thinners before and after surgery.

- **Trauma**

A person who has had a significant trauma (in a car crash, for example) is at great risk for **DVT** and **PE**. These patients are generally unable to move for long periods of time due to their injuries. Often they are severely ill and are unable to have blood thinners due to their injuries.

- **Medical Illness**

About 60% of **VTE** events are related to confinement to a hospital or nursing home. Medical conditions that carry a high risk for **VTE** in hospitalized patients include congestive heart failure, major respiratory illnesses, cancer, sepsis, inflammatory bowel disease, and acute neurologic disease (such as stroke).

Malignancy (cancer) carries a significant risk for **VTE**. Up to 30% of patients with cancer can develop a **DVT**. While any cancer can increase the risk of **DVT**, leukemias and lymphomas have a particular risk, as do lung and gastrointestinal cancers. The risk

of **DVT** is highest early after the diagnosis of cancer, and cancer can sometimes be diagnosed in patients who present with a **DVT** for initially unknown reasons.

- **Immobilization or Travel**

Bed rest or other immobilization is also associated with an increased risk of **VTE**. This has to do with blood “pooling” in the **veins** for long periods of time, a condition called “stasis”. Stasis of blood in the veins is the reason that people on long air flights or long drives are thought to have increased risk of **VTE**. This risk can mostly be erased by occasionally moving about during the travel and using knee-high elastic compression stockings. Older age, obesity, previous history of **VTE**, use of oral contraceptives and underlying blood clotting disorder increase the risk of travel-related clots.

- **Primary Blood Clotting Disorders**

There are several known genetic conditions that alter the presence or amount of **clotting factors** in the blood. These conditions often are associated with an increased risk of **DVT** or **PE**, but usually cause a problem only when another risk factor is also present. These existing genetic conditions include **antithrombin III (AT III) deficiency**, **protein C deficiency**, **protein S deficiency**, **Factor V Leiden mutation**, **anti-phospholipid antibody syndrome**, **prothrombin 20210A gene mutation**, **hyperhomocysteinemia**, **alterations in plasmin generation** and **increase in factors II, VIII, IX or XI**. The amount that each of these conditions affects **DVT** risk varies with the condition and with whether the patient has either one or two genes coding for the defect.

- **Oral Contraceptives and Hormonal Therapy**

Estrogen (female hormone) replacement, either in oral contraceptives (birth control) or in hormone replacement therapy, has been associated with an increased risk of **VTE**. The higher the estrogen amount, the higher the risk. Although it is less clear, progestin components in some contraceptives may also be related to an increased risk of **VTE**. The risk for **VTE** in women who take oral contraceptives is greater in women over 40, and in smokers. In general, oral contraceptives are discouraged in smoking women over 40, or in women with one of the genetic clotting disorders.

Although, the doses of estrogen used for post-menopausal replacement are about 1/6 of those used for contraception, there is a 2-4 fold increase in the risk of **VTE** in women who use them. However, the risk of replacement therapy must be kept in perspective, as it causes only about 2 new cases of **VTE** per 10,000 women per year.

- **Pregnancy**

There is an increased risk of **DVT** and **PE** in pregnancy, primarily due to a combination of changes in the blood clotting factors and compression of the pelvic veins by the fetus. There is also a risk of **VTE** after delivery. Once a mother has had a **DVT** during pregnancy, she is at increased risk for a recurrent **DVT** during subsequent pregnancies.

How does clot affect the vein?

After clot forms in a **vein**, **inflammation** occurs in the vein wall and in the clot itself. This **inflammation** leads to extension of the initial clot and clot organization. Over several weeks to months the clot will usually recanalize. **Recanalization** is a re-opening of the vein that was previously blocked by clot. This organization and re-opening of the **vein** causes damage to the **vein wall** and the **vein valves**. **Recanalization** does not always happen completely. The body has very complex pro-inflammatory and anti-inflammatory response systems. The extent to which these systems are activated and how they interact may have a role in how soon or how well the clot is organized and recanalized.

Does the vein return to normal after the clot resolves?

The answer to this question is generally no. The normal **vein wall** is very elastic and thin. It can change size to a great degree. After a **DVT**, the vein wall becomes stiff. This is due to breakdown of the **elastin** and **collagen fibers** in the vein wall. In addition to these changes, the vein wall also becomes fibrotic over time after a **DVT**. **Fibrosis** is a process of “toughening” of tissue, similar to what is seen in scar formation. This **fibrosis** can also affect the **vein valves** causing them to stop functioning properly. This can all lead to **veins** that are stiff, tough and scarred, with **valves** that don’t function properly, and to increased pooling of blood in the **vein**. These changes in the **vein wall** and the **vein valves** contribute to the **symptoms** experienced in patients long-term after **DVT**, which include **leg pain, aching, heaviness, fatigue, and swelling**. This collection of **symptoms** is referred to as **post-thrombotic syndrome (PTS)**. While not everyone gets **PTS**, wearing **compression stockings** for at least 2 years after getting a **DVT** is thought to prevent or decrease the severity of **PTS**.

Conclusion

DVT and **PE** are common conditions. The **risk factors** include both genetic and environmental factors. **DVT** and **PE** generally occur when 2 or more of these risk factors occur at the same time. Decreasing the risk of **DVT** and its consequences involves decreasing immobility, using appropriate **anticoagulation**, and wearing **compression stockings** when appropriate.