

# MEDIA GUIDE ON BLOOD CLOTS



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# Blood clots and the coagulation cascade

## What is a blood clot?

Blood has two components: cells and plasma. The cellular portion of blood includes red blood cells, white blood cells and platelets; platelets are circulating fragments of precursor cells (megakaryocytes) that play an important role in the clotting process.

Normally, circulating blood is a liquid suspension, and the liquid component is known as plasma. Plasma is mainly comprised of water, electrolytes, nutrients and vitamins, hormones, clotting factors, and proteins such as albumin and immunoglobulin. Plasma transports the substances it contains as it circulates throughout the body.<sup>1</sup>

A blood clot is a complex gel including both proteins and cells that forms when a blood vessel is damaged. Under normal circumstances, an injury in, or damage to, a blood vessel leads to formation of a blood clot; this process is known as hemostasis. Physiologically, blood clotting prevents excessive blood loss from a damaged blood vessel.<sup>2</sup>

## How does blood clot?

The normal clotting process, coagulation, involves a complex series of reactions including three components: blood vessels, platelets, and coagulation factors.<sup>2,3</sup> When vascular injury occurs, the circulating coagulation factors present in blood are sequentially activated in a “cascade.”<sup>4</sup> The clotting cascade also activates platelets and promotes formation of a platelet plug in the injured vessel.<sup>3</sup> The end result is a blood clot consisting of both a fibrin gel and platelets that creates a barrier over the injury site, and protects it until it heals. This process also activates a feedback system that regulates clot formation so that clotting is limited to the area of injury.<sup>2</sup>

When a blood vessel is injured, the physiologic steps involved to stop bleeding include:

- 1. Vascular injury.** An injured vessel immediately constricts to minimize blood loss and exposes the blood to tissue factor (TF). Exposure to TF leads to platelet adherence-activation and stimulation of the coagulation cascade. Thrombin is formed during the coagulation cascade, resulting in the fibrin strands that bind the clot.<sup>3</sup>
- 2. Platelet plugging.** Platelets do not normally adhere to the endothelium, the smooth inner surface of the blood vessel. However, with endothelial damage, platelets are activated and begin to clump at the site of damage. Once the activated platelets start to aggregate, they release several chemicals that reinforce a process that causes circulating platelets to become activated. These nearby platelets then adhere to the first layer of platelets. This process allows more and more platelets to rapidly aggregate at the injury site and form the platelet plug.<sup>2</sup>

**3. Coagulation.** Coagulation transforms circulating blood from a liquid suspension into a gel. These “normal” blood clots are part of the body’s healing process. The ultimate step in the formation of a blood clot is the conversion of fibrinogen, a large, soluble protein produced by the liver and normally always present in the blood, into fibrin, an insoluble, threadlike molecule that helps to seal the injured vessel.<sup>4</sup>

Although several feedback systems exist to limit coagulation, occasionally blood clots form due to inappropriate activation of the coagulation cascade. Low flow, endothelial injury, and pathologic activation of the coagulation system all predispose to VTE-related complications and inappropriate coagulation.<sup>5</sup>

## Blood clots in arteries and veins

Arteries are the muscular, high-pressure, high-flow vessels that deliver oxygen-rich blood pumped from the left ventricle of the heart to the rest of the body. Atherosclerotic plaque that damages the endothelium, and may narrow the artery, is the site of most arterial clotting (thrombosis). When the structure of the plaque becomes unstable (“plaque rupture”), the flowing blood comes in contact with the injured artery.<sup>6</sup> Currently, patients with atherosclerotic arterial disease are often treated with antiplatelet agents.<sup>7</sup>

Veins are lower-pressure vessels that carry deoxygenated blood away from the muscles and internal organs and back to the heart. A venous clot may limit blood return and can result in pain and swelling as the blood accumulates.<sup>8</sup> Venous clots are predominately formed by activation of the clotting cascade, and patients with, or at risk of, venous clots require anticoagulant drugs in order to prevent clot-related complications.<sup>8</sup>

## The formation of blood clots

The formation of a blood clot is a physiologically complex and balanced process. Body systems work to minimize the loss of blood at an injured site, while preventing the generation of clots elsewhere. Coagulation factors have a major role in establishing and strengthening blood clot formation via a series of cascading events. There are 2 branches of the coagulation cascade, referred to as the extrinsic and intrinsic pathways (see Fig 1). These pathways converge to the “Common Pathway,” which leads to the generation of thrombin, and subsequently formation of the fibrin mesh. The basic steps of physiologic coagulation are described below.

### STEP 1

As a blood vessel (or other tissue) is injured, tissue factor (TF) is exposed and results in the aggregation and activation of platelets at the injury site. These platelets begin to form a loose plug, and further stimulate the aggregation of other nearby circulating platelets.

### STEP 2

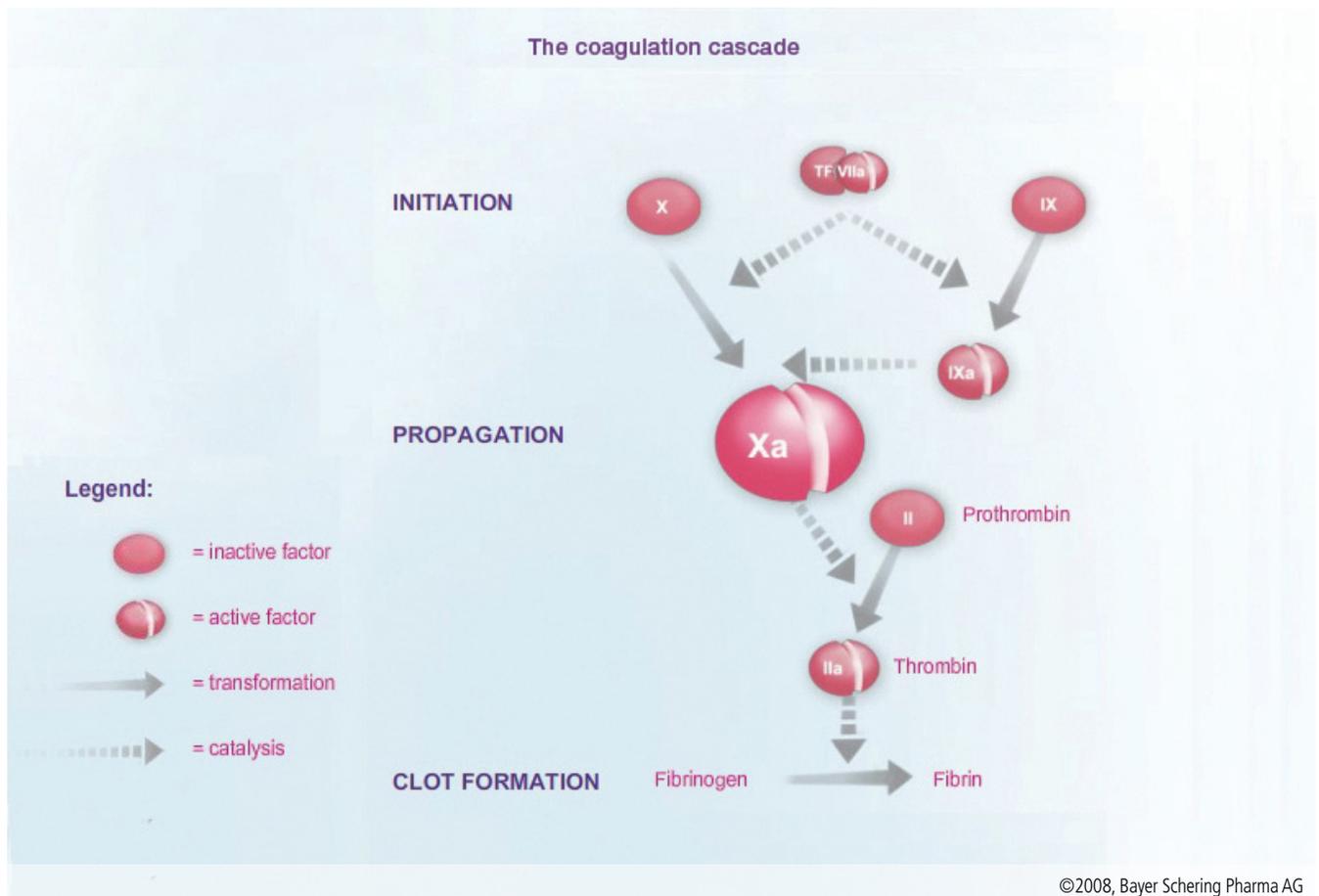
Tissue factor also activates blood coagulation factors involved in the Extrinsic Pathway. This leads to the initial activation of Factor X to Factor Xa (common pathway point) and results in the initial production of thrombin, then fibrin.

### STEP 3

The initial production of thrombin, and other local mediators, activates the Intrinsic Pathway, resulting in amplification of Xa production at the pathway point. Xa, in conjunction with Factor Va/phospholipids/ $Ca^{+2}$ , creates a burst of thrombin formation, resulting in further production of fibrin.

### STEP 4

The fibrin organizes into a stabilized meshwork, trapping platelets and other blood constituents, finalizing the production of the blood clot. It is recognized that though the coagulation process is outlined as a series of steps, in actuality, it is a series of overlapping, parallel running events.<sup>2,3</sup>

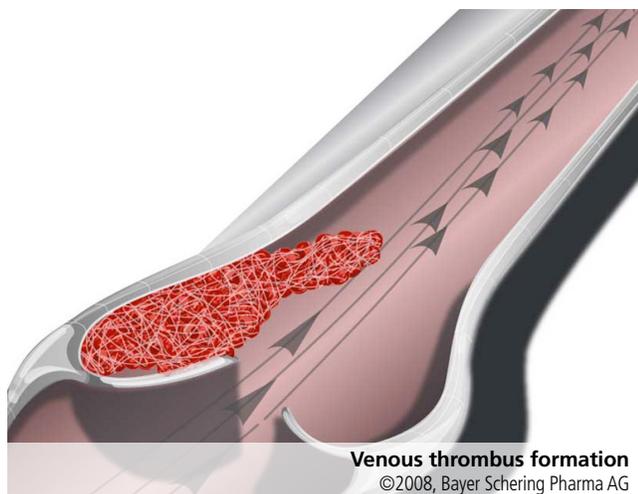


# Fast facts about venous blood clots

- ▶ Normally, blood clots (thrombi) form to prevent prolonged bleeding in response to injury to a blood vessel wall. The normal clot represents transformation of blood from a liquid suspension to a solid gel that serves to plug the site of the blood vessel injury.<sup>6</sup>
- ▶ A blood clot will dissolve naturally once the injury has healed. However, when activated inappropriately, the clotting process can lead to the formation of pathologic (abnormal) clots with potentially fatal consequences.<sup>6,10</sup>
- ▶ Pathologic venous blood clots (also known as venous thromboembolism, or VTE) include:
  - ▶ A **deep vein thrombosis (DVT)**, a blood clot in a deep vein (usually in the leg) that partially or totally blocks the flow of blood, which may lead to;
  - ▶ A **pulmonary embolism (PE)**, a blood clot in the lung(s) that can partially or totally block the flow of blood, creating a potentially life-threatening condition.
- ▶ Each year, it is estimated that more than 900,000 Americans have a VTE episode, of which, approximately one third are fatal.<sup>11</sup>
- ▶ People can be at risk to develop pathologic venous blood clots due to a variety of factors that include blood vessel injury, stasis, and increased genetic propensity for thrombosis, known as thrombophilia.<sup>5</sup>

# What is venous thromboembolism (VTE)?

Venous thromboembolism is a potentially deadly condition caused by abnormal (pathologic) blood clots that form in the veins. VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE).



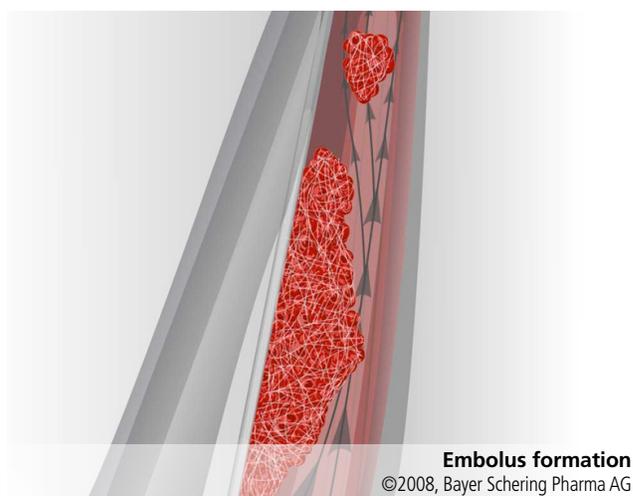
DVT occurs when blood clots in one of the large, deep veins in the lower leg or calf. Larger blood clots that substantially block the flow of blood may cause pain and swelling in the affected leg. Other symptoms can include redness and feeling of warmth in the leg.<sup>8</sup> Blood clots that only partially block the flow of blood often produce no symptoms; these asymptomatic episodes account for approximately half of all DVT cases.<sup>7</sup>

Pulmonary embolism (PE) is a serious complication of DVT. A PE most commonly occurs when part of a clot dislodges from a lower extremity and is carried along to the pulmonary arterial circulation system, where it can partially or completely block blood flow. Typically, symptomatic PE causes difficulty breathing, rapid heart rate, chest pain, and low blood pressure. Some patients cough up blood, while others faint.<sup>12</sup> When PE occurs with large clots or multiple clots, or when the patient already has preexisting heart or lung disease, the event may be fatal.<sup>10</sup>

## Prevalence of VTE

In the United States, VTE is the third leading cause of cardiovascular death.<sup>13</sup> It accounts for approximately 250,000 hospital admissions annually.<sup>11,14</sup> Each year, it is estimated that more than 900,000 Americans have a VTE episode, of which approximately one third are fatal.<sup>11</sup>

In a portion of Europe, the figures are similar. More than 465,000 cases of DVT, 295,000 cases of PE, and 370,000 VTE-related deaths occur annually.<sup>15</sup> The number of venous blood clot-related deaths in the European Union is estimated to be more than double the number of deaths due to AIDS, breast cancer, prostate cancer, and motor vehicle accidents combined.<sup>15</sup>



## Risk factors for VTE

People most likely to experience a VTE include those who have undergone major surgery, the elderly, pregnant women, and those using certain medications or therapies. Prolonged immobility and chronic medical conditions such as heart disease and cancer also increase the risk of developing blood clots.<sup>12</sup>

Patients undergoing major orthopedic surgery are at high risk for VTE. In the United States, approximately 800,000 individuals have hip and knee replacement surgery each year, and the most common reason these patients are re-hospitalized is complications caused by blood clots.<sup>7</sup>

In addition to the risks posed by major surgery, there are a number of other risk factors for developing VTE.<sup>7</sup>

**Age:** Patients over 40 years of age are at a significantly increased risk compared with younger patients, and this risk roughly doubles with each subsequent decade.<sup>16</sup>

**Pregnancy:** Pregnancy causes hormonal changes that can raise the risk of developing a blood clot. Pregnant women have a five-fold increased risk of developing a DVT compared with non-pregnant women, and risk is even greater during the postpartum period. Other conditions, such as diabetes or obesity, can also magnify the risk of DVT during pregnancy.<sup>17</sup>

**Obesity:** Being obese can also increase the risk of VTE.<sup>17</sup>

**Air Travel:** VTE has been described as “economy-class syndrome” because of the risks associated with venous blood clots during long-distance air travel.<sup>16</sup> One study showed that travel is associated with a nearly 2-fold higher risk for VTE, and that the risk increases with longer distances traveled.<sup>18</sup>

**Hormones:** The risk of VTE also can increase with the use of certain medications, particularly oral contraception that contains estrogen. Similarly, women receiving hormone-replacement therapy (HRT) are at an increased risk for VTE. Studies suggest that women with a history of VTE who are using HRT are at greater risk of recurrence than those with a similar history but who are not taking hormones.<sup>16</sup>

**Cancer:** Cancer and cancer treatment are also well-recognized risk factors for VTE. Advanced cancers are associated with a high incidence of VTE, especially cancers of the breast, lung, brain, pelvis, rectum, pancreas, and gastrointestinal tract. The risk of VTE may be increased further by treatment, including surgery, chemotherapy, and hormonal therapy.<sup>16</sup>

**Hereditary:** Some individuals will develop venous blood clots because of abnormalities in the coagulation cascade. These hereditary disorders, known as thrombophilias, affect one or more of the clotting factors and lead to the formation of blood clots. Hereditary thrombophilias include Factor V Leiden, a clotting disorder common among individuals of European descent, and genetic mutations, such as the prothrombin gene mutation G20210A.<sup>16</sup> Some individuals have abnormally high levels of the amino acid homocysteine in the blood that may increase their risk of PE and VTE.<sup>16</sup> Other genetic conditions include protein C and S deficiencies, as well as antithrombin deficiencies.<sup>19</sup>

## Symptoms of VTE

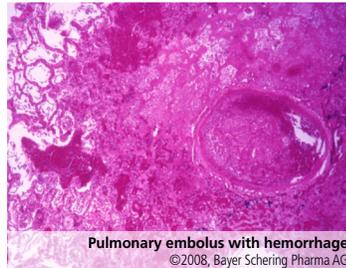
VTE is generally a silent disease associated with a low frequency of clinical symptoms. The true prevalence of VTE is underestimated because many cases are asymptomatic, or not apparent clinically. By the time DVT is diagnosed, a PE has already occurred in an estimated 50% of patients. If there are symptoms, they are usually nonspecific.<sup>20</sup>

### Deep vein thrombosis

The typical symptoms of DVT include leg pain, swelling, and warmth in the affected limb. A physical examination might also reveal distention of other veins.<sup>8</sup>

### Pulmonary embolism

Symptoms of PE include shortness of breath, rapid pulse, sweating, chest pain, and lightheadedness or fainting; symptoms of DVT may also be present.<sup>21</sup>



## Diagnosing VTE and PE

The American Academy of Family Physicians (AAFP) and the American College of Physicians (ACP) published clinical practice guidelines summarizing the current approaches to diagnosing VTE. The groups recommend that validated prediction models be used to estimate a patient's probability of having a VTE. One model, known as the Wells clinical model, assigns a point system to a number of risk factors, signs, and symptoms; the total of these points characterizes the patient's degree of risk for VTE.<sup>22</sup>

For patients with a high likelihood of having a PE as determined by the Wells prediction model, other imaging tests are essential.<sup>22</sup> These tests include ventilation-perfusion scans, computed tomography (CT), and pulmonary angiography. Advances in the field of CT, including the development of powerful multidetector-array scanners, have led to the emergence of CT scanning as an important diagnostic technique in suspected PE. Like pulmonary angiography, CT scanning shows the emboli directly.<sup>22</sup> The advantage of CT is that it is noninvasive, inexpensive, and widely available.

Another imaging procedure for diagnosing blood clots in the deep veins of the leg is a venogram. This test is an X-ray of the deep veins and allows clinicians, through the injection of a special dye known as contrast material, to see the blood as it flows through the veins. The goal of venography is to help distinguish blood clots from other obstructions in the veins.<sup>22</sup>

# Preventing and treating VTE

## Prevention

Because DVT can partly or completely block blood flow and lead to PE, prevention is vital. To reduce the risk of DVT, physicians recommend that people maintain an active lifestyle and exercise regularly, manage weight gain, quit smoking, and lower blood pressure. In addition, women on birth control or hormone replacement therapy should talk with their doctor about their risk for VTE. For patients undergoing surgery, surgeons will review medical history to help assess a patient's risk for DVT and determine what measures are necessary to prevent it. These may include prescription anticoagulation, mechanical devices, compression stockings, and mobilization. The best way to reduce the risk of PE is to prevent DVT.<sup>10</sup>

In 2008 the Surgeon General issued a call to action to prevent DVT and PE. While there is a lot known about how to prevent and minimize the impact for those patients who suffer from VTE, the knowledge is not applied consistently.<sup>17</sup> According to Dr. Elizabeth Nabel, the former director of the National Heart, Lung, and Blood Institute, there are few public health problems as serious as DVT and PE, and innovative research by investigators committed to finding new ways to prevent and treat these conditions is still needed.<sup>17</sup>

## Treatment

The goals of VTE treatment are the prevention of clot formation, the prevention of PE, and the prevention of recurrent thrombosis.<sup>23</sup> The current cornerstone of medical therapy is anticoagulation, including drugs such as heparin and warfarin, as well as newer agents. Anticoagulants are used to halt the progression or growth of the blood clot.<sup>24</sup>

Heparin is a naturally occurring substance that inhibits the clotting cascade. It can come in high, standard unfractionated heparin, or low-molecular-weight fractionated heparin, and both forms must be administered through injection.<sup>23</sup> Heparin prevents the formation of new blood clots and the growth of existing blood clots by binding to antithrombin.<sup>23</sup>

Warfarin is the most commonly prescribed oral anticoagulant and is frequently given for long-term treatment of recurring VTE.<sup>24</sup> Warfarin is a vitamin K antagonist (VKA) and works by interfering with the synthesis of various vitamin K dependent coagulation factors in the liver, including Factors II, VII, IX, and X.<sup>24</sup>

## New oral therapeutic options in development

### Inhibiting Factor Xa

Factor Xa has emerged as an attractive target for potential new anticoagulant agents due to its pivotal point in the coagulation cascade, where it stimulates the production of thrombin, the enzyme that promotes clot formation; Factor Xa leads to the formation of thrombin.<sup>25</sup>

Inhibition of Factor Xa interrupts both the intrinsic and extrinsic pathway of the blood coagulation cascade, that may help regulate the action of thrombin and the development of blood clots.<sup>25</sup>

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