DEEP VEIN THROMBOSIS (DVT) and PULMONARY EMBOLISM (PE)

EXECUTIVE SUMMARY

- A venous thrombosis (VTE) is a blood clot (thrombus) that forms within a vein. Most often, the blood clot develops in the deep veins of the leg or pelvis, known as deep vein thrombosis (DVT). If the clot, or a part of it, breaks off from the site of formation and travels through the circulatory system, an embolism may occur. When the clot lodges in the lung this is known as pulmonary embolism (PE), a life-threatening condition.[1]

- Combined, DVT and PE are estimated to be the third most common cardiovascular disorder after coronary heart disease and stroke.[2] Over 750,000 DVT and PE events are estimated to occur annually in six major EU countries (France, Germany, Italy, Spain, Sweden, UK)[3] and over 900,000 events occur annually in the US.[4]

- VTE is a serious complication after major orthopaedic surgery, such as total knee replacement or total hip replacement.[5]

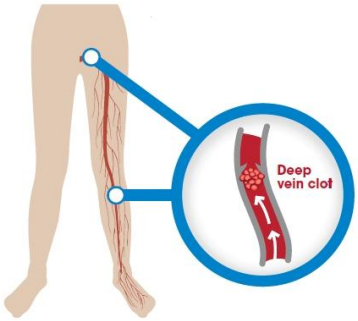
- A DVT or PE can develop in almost anyone but common risk factors include age, prolonged immobility and a history of previous blood clots.[1]

- Anticoagulant treatment is the standard therapy for DVT and PE treatment, preventing new blood clots from forming and existing ones from getting any bigger. [5] Anticoagulants may provide up to a three-fold reduction in the recurrence of thromboembolic events.[6]

Boehringer Ingelheim

Last updated: October 2014

What are DVT and PE?

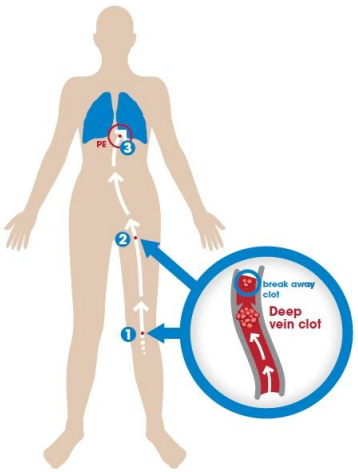


Deep vein thrombosis

DVT results from the formation of a blood clot (thrombus) inside a deep vein, usually in the leg or pelvis, which either partially or totally blocks the flow of blood in the vein.[1] It increases the risk of recurring clots and may cause serious complications such as PE or post-thrombotic syndrome (PTS).[1, 7] Approximately one third of patients with symptomatic DVT also develop PE.[8]

Pulmonary embolism

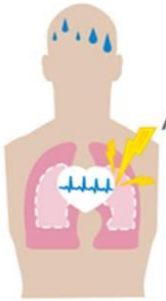
A PE occurs when a deep vein clot, or part of it, breaks loose and travels to one of the lungs where it may block circulation. It is a serious and growing complication. PE develops suddenly, often without warning, and can be fatal in up to 30% of cases within three months.[9] It is considered to be the leading cause of preventable death in hospital.[10] Those who survive can be affected by permanent damage to the affected lung and other vital organs as oxygenated blood cannot be circulated.[11] PE may also lead to complications such as chronic thromboembolic pulmonary hypertension (CTEPH).[12]



What are the symptoms?

The majority of people with DVT do not feel any symptoms. If there are symptoms they usually occur in one leg only. People with DVT may experience swelling, pain and tenderness, prominent veins and increased skin temperature.[13]

People suffering from PE may experience acute shortness of breath, chest pain, sweating and rapid heart rate.[13, 14]



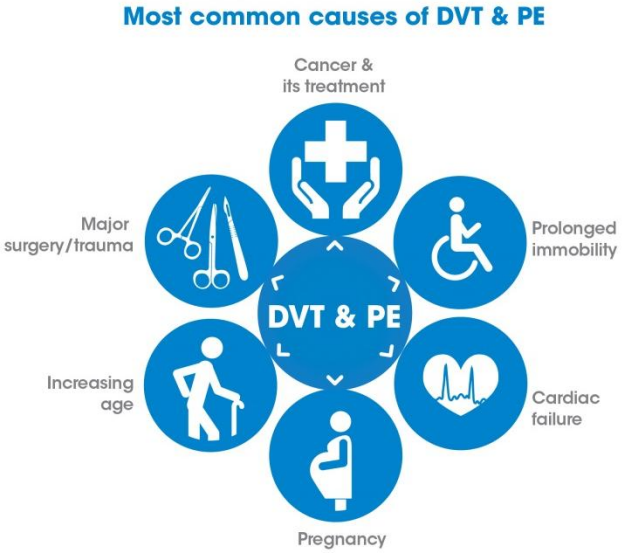
PULMONARY EMBOLISM
Acute shortness of breath
Chest pain
Sweating
Rapid heart Rate

DEEP VEIN THROMBOSIS
Swelling
Pain and Tenderness
Change in colour of skin
Skin warm to touch

What are the risk factors?

Although a venous blood clot can develop in almost anyone, there are a number of factors and trigger events that can increase the risk of DVT and PE, including: [1, 14–16]

- Increasing age
- Prolonged immobility
- Stroke or paralysis
- Previous VTE
- Cancer and its treatment
- Major surgery
- Trauma
- Obesity
- Cardiac failure
- Pregnancy
- Venous insufficiency (poor circulation of the blood)



Long-term complications of DVT and PE

Many patients fully recover from DVT and PE, however there are a number of long-term complications that can cause substantial illness and pose a high economic burden on societies.

Recurrent blood clots

Once a patient has had a first DVT or PE, for most people the risk of suffering a second one is likely to always remain.[17] Up to one quarter of patients with DVT and PE will experience a recurrent clot within five years. [18] Data has shown that the risk of recurrent clots can increase cumulatively in patients who are not treated with standard therapy from 11% after one year to up to 40% after 10 years.[18]

Post-thrombotic syndrome

Post-thrombotic syndrome is a common complication of DVT. It results from damage to the valves in the deep veins, causing pain, redness, and thickening of the skin. It can be debilitating and may lead to chronic leg ulceration. Up to 60% of patients with DVT develop post-thrombotic syndrome, frequently occurring within two years.[19] Graduated elastic compression stockings or pneumatic compression boots and anticoagulant therapy are often used to reduce the risk of post-thrombotic syndrome after DVT.[20]

Chronic thromboembolic pulmonary hypertension

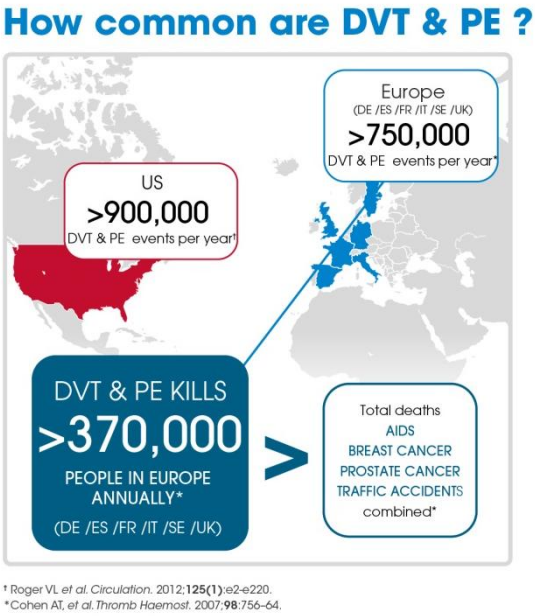
Chronic thromboembolic pulmonary hypertension is a serious complication among patients who have suffered from PE.[12] Chronic thromboembolic pulmonary hypertension is a form of high blood pressure in the blood vessels of the lungs. It can be caused by old blood clots blocking blood flow in the lungs or by the progressive narrowing of healthy blood vessels.[21] Approximately 4% of patients may develop this condition within two years of suffering from a PE.[12]

DVT and PE - an increasing problem

DVT and PE are collectively estimated to be the third most common cardiovascular disorder after coronary heart disease and stroke.[2] Over 750,000 DVT and PE events are estimated to occur annually in six major EU countries (France, Germany, Italy, Spain, Sweden, UK)[3] and over 900,000 events occur annually in the US.[4]

Figures for the six European countries show that venous thrombotic events kill more people than AIDS, breast cancer, prostate cancer and traffic accidents combined.[3]

Undiagnosed DVT and PE may result in significant additional burden on healthcare systems and lead to considerable underestimation of number of events, and ultimately deaths, worldwide.[3]

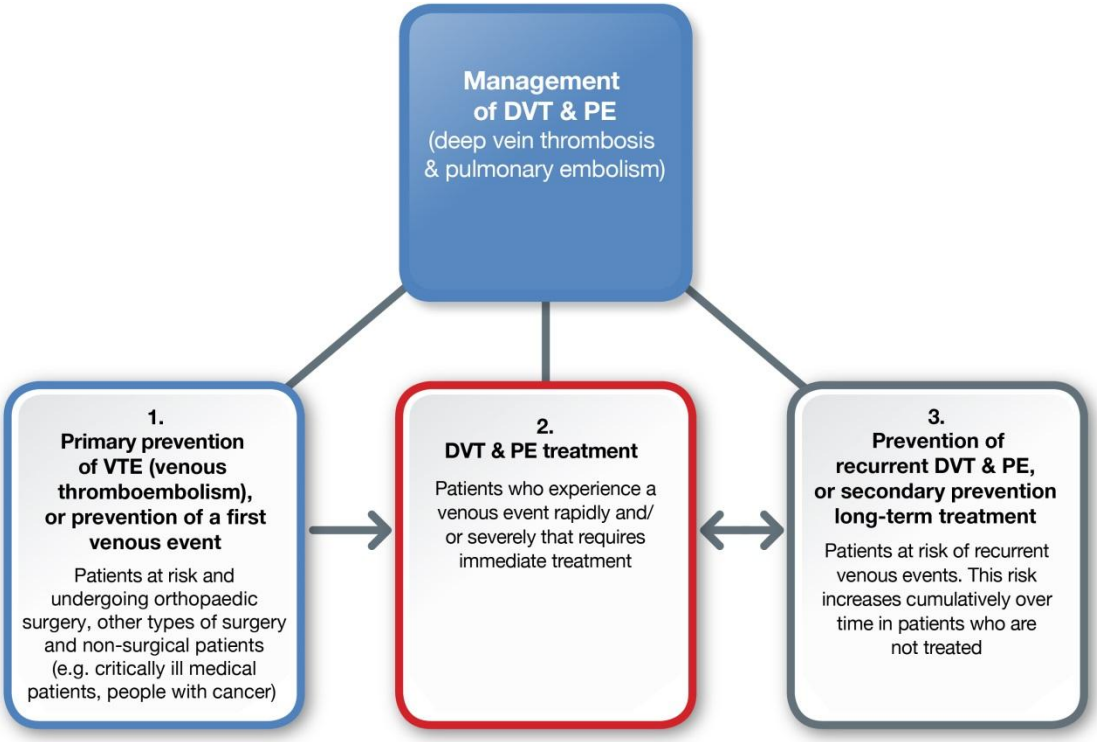


The cost of DVT and PE

The human cost of DVT and PE is immeasurable and has significant implications on patients' lives, their families, healthcare systems and society as a whole.

Given their prevalence, associated morbidity, mortality and chronic complications, DVT and PE are costly conditions that put a considerable burden on healthcare systems worldwide. Annual costs are estimated to be more than €3.07 billion in Europe for total direct costs associated with DVT and PE, [22] and up to $15.5 billion in the US for DVT and PE diagnosis and treatment.[23]

Current management of DVT and PE



There are treatment options for people at every stage of DVT and PE:

- Protection from an initial clot, known as primary prevention
- Treating a clot that has already developed
- Prevention against recurrent clots, known as secondary prevention and long-term treatment

Primary prevention of VTE – prevention of a first event

The latest guidelines from the American College of Chest Physicians (ACCP) provide extensive recommendations for the primary prevention of VTE in several patient groups including:[5, 24]

- Patients undergoing orthopaedic surgery (e.g. of the hip or knee)
- Non-orthopaedic surgery patients (e.g. patients undergoing general, GI, urological, gynaecologic, bariatric, vascular, plastic, or reconstructive surgery)
- Non-surgical patients (e.g. critically ill medical patients, patients with cancer, those chronically immobilised, people who travel long-distances)

Recommendations for patients undergoing orthopaedic surgery

VTE is a common complication associated with major orthopaedic surgery. Anticoagulation therapy is effective in preventing venous blood clots in patients undergoing total knee replacement or total hip replacement. The ACCP CHEST guidelines highlight the benefits of one of the following treatments:[5,24]

- Novel oral anticoagulants e.g dabigatran etexilate, rivaroxaban or apixaban
- Low-molecular weight heparin (LMWH)
- Low-dose unfractionated heparin (LDUH)
- Fondaparinux
- Adjusted-dose vitamin K antagonist (VKA)
- Acetylsalicylic acid (ASA)
- An intermittent pneumatic compression device

Dabigatran etexilate, a direct thrombin inhibitor, was the first approved treatment of a new generation of novel oral anticoagulants. Direct thrombin inhibitors work by specifically and selectively blocking the activity of thrombin – the central enzyme in clot formation.[25, 26]

In 2008 the European Commission granted EU approval for dabigatran etexilate for the primary prevention of VTE in adults who have undergone elective total knee or hip replacement surgery.[27] Results from the RE-NOVATE®[28], RENOVATE II®[29] and RE-MODEL™[30] trials show that dabigatran etexilate is as effective as enoxaparin, a low-molecular weight heparin, in preventing VTE events and their consequences after total knee or hip replacement. In addition, treatment with dabigatran etexilate resulted in a low incidence of major bleeding events.[28-30]

Recommendations for non-surgical patients and patients undergoing non-orthopaedic surgery

Treatment recommendations for other patients depend on the respective patient type, surgery type and the presence of risk factors for both thrombosis and bleeding. Treatment options include anticoagulant therapy e.g. low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH) or fondaparinux, elastic compression stockings or pneumatic compression devices, or no treatment at all.[24]

DVT and PE treatment

Data has shown that up to 30% of people who experience a PE die within three months.[9] Immediate treatment is therefore crucial. There are different treatment options for DVT and PE. Usually, initial therapy is started with an injectable and fast-acting anticoagulant, which is then followed by an oral anticoagulant. In case of major PE, systemic thrombolysis can also be considered.[5, 24]

The ACCP CHEST guidelines recommend anticoagulation treatment with LMWH, fondaparinux or unfractioned heparin. Additionally, an oral VKA should be introduced on the first day of treatment. The parallel treatment should continue for a minimum of five days and until the patients' blood levels show that the appropriate therapeutic level for VKA (international normalised ratio between 2 and 3) has been achieved.[31] In addition, the ACCP CHEST guidelines highlight that treatment of DVT and PE with a novel oral anticoagulant such as dabigatran, in addition to being less burdensome to patients, may prove to be associated with better clinical outcomes than VKA and LMWH therapy. [31]

Treatment duration is typically for three months. Factors that impact management and treatment duration include:

- Severity of symptoms
- Location and extension of DVT (above or below the knee)
- Presence of risk factors for thrombosis including prior DVT or PE
- Presence of risk factors for bleeding
- Contraindications to treatment

For patients with DVT, compression stockings are also recommended to help prevent post thrombotic syndrome.[31]

In June 2014, dabigatran etexilate was approved by the European Commission for the treatment and prevention of recurrence of DVT and PE. [27] The U.S. Food and Drug Administration (FDA) approved dabigatran etexilate for DVT and PE patients in April 2014.[32] The approvals were based on results from three robust phase III clinical trials that demonstrated the efficacy of dabigatran etexilate in the treatment and prevention of repeat DVT and PE compared to warfarin (RE-COVER™, RE-COVER II™, RE-MEDY™) and one trial compared to placebo (RE-SONATE™), involving close to 10,000 patients.[33-35] Data also showed that treatment with dabigatran etexilate had significantly lower bleeding rates compared to warfarin.[33-35]

Prevention of recurrent DVT and PE, or secondary prevention and long-term treatment

Data has shown that the risk of recurrent DVT and PE can increase cumulatively in patients who are not treated with standard therapy from 11% after one year to up to 40% after 10 years.[18] Therefore, long-term prevention is essential. Within the first two years, the risk of recurrence is greatest.[17] Treatment duration is often between three and six months, but due to the high likelihood of DVT and PE recurrence, long-term anticoagulant treatment beyond three months should be considered in patients who are at risk. Treatment decisions should be tailored to the patient and their individual risk factors, and physicians should weigh up the benefit-risk profile of extended treatment versus the risk of bleeding on a regular basis. [36]

Risk factors for a recurrent DVT and PE include:

- Number of previous DVT and PE events
- Location of initial DVT and PE
- Original trigger event (unprovoked or not)
- Patient characteristics including age, sex and weight

The availability of novel oral anticoagulants that – in contrast to traditional vitamin K antagonists – do not require regular blood testing and are not associated with numerous limitations like food-interactions or drug-interactions, may help to improve long-term treatment to better prevent recurrent events. [37]

References

1. Centers for Disease Control. DVT and PE Facts Available at: http://www.cdc.gov/ncbddd/dvt/facts.html Last accessed October 2014
2. Goldhaber SZ. Pulmonary embolism thrombolysis: a clarion call for international collaboration. *J Am Coll Cardiol*. 1992;**19**:246-247
3. Cohen AT. *et al.* Venous thromboembolism (VTE) in Europe. *Thromb Haemost*. 2007;**98**:756–64
4. Roger VL. *et al*. Heart disease and stroke statistics—2012 update: A report from the American Heart Association. *Circulation*. 2012;**125(**1):e2-e220
5. Falck-Ytter Y. *et al* . Prevention of VTE in Orthopedic Surgery Patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012 ;**141**(2)(suppl): e279S-e325S
6. Brandjes D. *et al.* Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med.* 1992;**327**:1485–9
7. Kahn SR. The post-thrombotic syndrome. *Hematology Am Soc Hematol Educ Program*. 2010;**2010:**216-20
8. White RH. The Epidemiology of Venous Thromboembolism *Circulation*. 2003;**107:**I-4-I-8
9. Heit JA. *et al*. Predictors of Survival after Deep Vein Thrombosis and Pulmonary Embolism. *Arch Intern Med*. 1999;**159**:445-453.
10. BMJ Best Practice. VTE Prophylaxis. Available at: http://bestpractice.bmj.com/best-practice/monograph/1087.html Last accessed October 2014
11. National Heart, Lung and Blood Institute. What is pulmonary embolism? Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/pe/ Last accessed October 2014
12. Pengo V. *et al.* Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med.* 2004;**350**:2257-64
13. Scottish Intercollegiate Guidelines Network. Prevention and management of venous thromboembolism. Available at: www.sign.ac.uk/pdf/qrg122.pdf Last accessed October 2014
14. Medline Plus. Pulmonary embolus. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/000132.htm Last accessed October 2014
15. Goldhaber SZ. Risk factors for venous thromboembolism. *J Am Coll Cardiol*. 2010;**56**:1-7
16. Nijkeuter M. *et al.* The natural course of hemodynamically stable pulmonary embolism: clinical outcome and risk factors in a large prospective cohort study. *Chest.* 2007;**131:** 517–23
17. The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. 2008.
18. Prandoni P. *et al*. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. *Haematological*. 2007;**92**(02):199–205
19. Ashrani AA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis.* 2009; **28**: 465-76
20. Vazquez SR *et al*. Postthrombotic syndrome. *Circulation.* 2010;**121:**e217-9
21. Pulmonary Hypertension Association. Chronic Thromboembolic Pulmonary Hypertension. Available at: http://www.phassociation.org/page.aspx?pid=3833. Last accessed October 2014
22. Coalition to Prevent VTE. The Burden of VTE. Available at: http://www.coalitiontopreventvte.org/INDEX_CFM/T/THE_BURDEN_OF_VTE/OBJECTID/866876ED_1422_16B3_78D29387FBC3/VID/9E7D3566_C09F_296A_6111019937AE/CONTAINERID/666415AA_C09F_296A_61DB66942768/DISPLAYMETHOD/DISPLAY_ARTICLE.HTM Last accessed October 2014
23. Medscape. Anticoagulation Therapy for Venous Thromboembolism. *Medscape General Medicine*. 2004;**6**,(3)5
24. Guyatt GH *et al*. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. *2012;**141**(2_suppl):7S-47S*
25. Di Nisio M, *et al*. Direct thrombin inhibitors. *N Engl J Med* 2005;**353**:1028-40
26. Sorbera LA, *et al.* Dabigatran/Dabigatran etexilate. *Drugs Future.* 2005; **30**:877-885
27. Pradaxa® Summary of Product Characteristics. 2014
28. Eriksson BI. *et al.* Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet.* 2007;**370**:949–56
29. Eriksson BI. *et al*. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double blind, non-inferiority trial. *Thromb Haemost*. 2011;**105**(4):721-9
30. Eriksson BI. *et al*. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 2007;**5**:2178–85
31. Kearon C. *et al.* Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST*. 2012;141(2_suppl):e419S-e494S
32. Pradaxa® Prescribing Information. 2014 Available at: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf Last accessed October 2014
33. Schulman S. *et al.* Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;**361**:2342–52
34. Schulman S. *et al.* Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;**129**:764-772
35. Schulman S. *et al*. Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism. *N Engl J Med* 2013;**368**:709–18
36. Kearon C and Aki EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood 2014;**123**:1794–1801
37. Schulman S. Extension of anticoagulation after venous thromboembolism. *Hämostaseologie*. 2008:**3**:110-119