Please note that in this factsheet we will be referring apixaban, dabigatran, edoxaban and rivaroxaban as direct-acting oral anticoagulants (DOACs). We recognise that in practice both DOAC and non-vitamin K antagonist oral anticoagulant (NOAC) are used interchangeably.

Definition
The NICE Clinical Knowledge Summary (CKS) Pulmonary embolism defines pulmonary embolism (PE), the different classifications of PE, and terminology used to describe PE in the following way:

Pulmonary embolism is a condition in which one or more emboli, usually arising from a thrombus (blood clot) formed in the veins (or, rarely, in the right heart), are lodged in and obstruct the pulmonary arterial system.

- **Provoked pulmonary embolism** is a pulmonary embolism associated with a transient risk factor such as significant immobility, surgery, trauma, and pregnancy or puerperium. The combined contraceptive pill and hormone replacement therapy are also considered to be provoking risk factors. These risk factors can be removed, reducing the risk of recurrence.

- **Unprovoked pulmonary embolism** is a pulmonary embolism occurring in the absence of a transient risk factor. The person may have no identifiable risk factor or a risk factor that is persistent and not easily correctable (such as active cancer or thrombophilia). Because these risk factors cannot be removed, the person is at an increased risk of recurrence.

Deep vein thrombosis is the term used to describe the formation of a thrombus in a deep vein, usually in one of the legs.

Venous thromboembolism is a term used to encompass both pulmonary embolism and deep vein thrombosis.

The term ‘thrombus’ is used to describe a blood clot that forms in a vessel. The term ‘embolus’ is used to describe an object that travels through the blood vessels; this is often a thrombus but may be an air bubble or other materials. An embolus will travel until it reaches a vessel that it is too small for it to fit through.

Prevalence and incidence
Reported deaths due to PE fell by 30 percent in the period 2008 to 2012. The British Lung Foundation suggest that this drop may be due to people being risk assessed on admission to hospital, increased awareness of the causes of PE and improvements in oral contraceptives. Over the same period emergency hospital admissions for PE rose by 30 percent.

Based on the Health and Social Care Information Centre’s Hospital Episode Statistics, 47,594 cases of PE were reported in the UK over a one-year period between 2013 and 2014.

Studies in the US and Europe have reported the annual incidence of PE to be 4 to 21 per 10,000 inhabitants. This variation is due to some of the data being clinical and some being from post mortems. It should be noted that clinical data may underestimate the true incidence of PE, whereas post-mortem data may overestimate it because clinically insignificant pulmonary emboli are detected.
An epidemiological model constructed to assess the number of venous thromboembolism (VTE) events and associated morbidity and mortality in Europe estimated that over 295,000 cases of PE occur every year, in six European countries (with a total population of 300 million).\(^5\)

**Signs and symptoms**
If not treated urgently PE can be life threatening. The NHS advise people to see their GP if:
- they feel pain in their chest or upper back
- they are have difficulty breathing
- they are coughing up blood.
(They also note that redness and swelling in one leg (usually the calf) are symptoms of a deep vein thrombosis [DVT]).

People should call 999 or go to the emergency department if:
- they have severe difficulty breathing
- their heart is beating very fast
- someone has passed out.\(^6\)

In the following *Anticoagulation UK video*, Sara speaks about her experience of colon cancer and how during her treatment, she developed breathlessness which turned out to be a PE.

**Causes/risk factors**
Although some emboli may originate from the right ventricle, veins of the abdomen or upper extremities, PE is usually caused by clots that form in the deep venous system, usually the legs. Part or all of these clots then break off, form emboli and travel to the lungs.\(^7\) This makes deep vein thrombosis (DVT) a major risk factor for PE. A model called Virchow's triad (Figure 1) outlines three main causes of DVT and PE.\(^8\)
Vessel wall damage – this describes damage to the endothelial cells that line the veins, usually at the valves. This can be caused by trauma, previous DVT, surgery, and central venous catheterisation.

Venous stasis (or lack of movement within the veins) – this can cause blood to pool and clot. Venous stasis is linked to age over 40 years, immobility, general anaesthesia, paralysis, spinal cord injury, myocardial infarction, prior stroke, varicose veins, advanced congestive heart failure, and advanced chronic obstructive pulmonary disease (COPD). Pooling of blood leads to damage of the valves which can further increase the risk of thrombus due to vessel wall damage.

Hypercoagulability (or an increased tendency for blood to clot) This can be caused by cancer, high oestrogen levels (oral contraceptives, hormone replacement, obesity or pregnancy), inflammatory bowel disease, sepsis, blood transfusion and inherited thrombophilia. More information about thrombophilia can be found on the NHS Thrombophilia page.

Figure 1. Virchow’s triad which outlines three main causes of DVT and PE.

Risk factors for PE can be split into major risk factors and other risk factors. These are outlined in the NICE CKS Pulmonary embolism, Risk factors. Information about alternative sources of emboli can also be found under Pulmonary embolism, Sources of emboli.

The 2019 European Society of Cardiology (ESC) Guidelines on Acute Pulmonary Embolism (Diagnosis and management of) also includes section 2.2 Predisposing factors.
Transient risk factors for venous thrombosis are shown in Table 1 below.\textsuperscript{9,10,11}

<table>
<thead>
<tr>
<th>Strong risk factor (odds ratio &gt;10)</th>
<th>Moderate risk factor (odds ratio 2-9)</th>
<th>Weak risk factor (odds ratio &lt;2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip or leg fracture</td>
<td>Arthroscopic knee surgery</td>
<td>Bed rest &gt;3 days</td>
</tr>
<tr>
<td>Hip or leg joint replacement</td>
<td>Congestive heart or respiratory failure</td>
<td>Immobility due to sitting (eg, prolonged road or air travel)</td>
</tr>
<tr>
<td>Major general surgery</td>
<td>Central venous lines</td>
<td>Increasing age</td>
</tr>
<tr>
<td>Major trauma</td>
<td>Hormone replacement therapy</td>
<td>Laparoscopic surgery (eg, cholecystectomy)</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>Malignancy</td>
<td>Obesity</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptive therapy</td>
<td>Pregnancy (antepartum)</td>
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<tr>
<td></td>
<td>Paralytic stroke</td>
<td>Varicose veins</td>
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<td></td>
<td>Postpartum</td>
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<tr>
<td></td>
<td>Previous venous thromboembolism</td>
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<tr>
<td></td>
<td>Thrombophilia</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Transient risk factors for venous thrombosis \textsuperscript{9,10,11}

Pathophysiology (mechanism of disease)
In PE, emboli which have become trapped in the pulmonary vasculature obstruct the pulmonary circulation and increase pulmonary vascular resistance. This can have an impact on heart function and in particular, the right ventricle.\textsuperscript{8}

The effect that a PE has on a person depends on the extent to which circulation is obstructed (which is affected by the size of the embolism), the duration of time that circulation is obstructed and patient factors (such as pre-existing cardiopulmonary disease or frailty).\textsuperscript{12}

The following article looks at the pathophysiology of PE in more detail:
Riedel M. \textit{Acute pulmonary embolism 1: pathophysiology, clinical presentation, and diagnosis}. \textit{Heart}. 2001; 85:229-240

Pathophysiology is also covered in section 2.4 Pathophysiology of the 2019 ESC \textit{Guidelines on Acute Pulmonary Embolism (Diagnosis and management of)}.

Long term effect of pulmonary embolism: Post-pulmonary embolism syndrome\textsuperscript{13,14}
As many as 50 percent of patients report long term sequelae after pulmonary embolism. Post-pulmonary embolism syndrome has been defined by suboptimal cardiac function, pulmonary artery flow dynamics, or pulmonary gas exchange at rest or during exercise, in combination with dyspnoea, decreased exercise tolerance, or diminished functional status or quality of life, without an alternative explanation.
Diagnosis/detection
Determining the likelihood of PE is usually based on clinical presentation and symptoms such as dyspnoea (breathlessness), tachypnoea (fast breathing), or chest pain which are present in more than 90 percent of patients with PE.\textsuperscript{15} Diagnosis is then made in secondary care.

When to suspect PE is summarised in the NICE CKS \textit{Pulmonary embolism, When to suspect PE}.

Diagnosis is covered in more detail in the following guidelines:

- NICE clinical guideline \textit{Venous thromboembolic diseases: diagnosis, management and thrombophilia testing (NG158)} which offers recommendations on the \textit{Diagnosis and Initial Management} for pulmonary embolism, from point 1.1.15.

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Prognosis and complications
Risk stratification of patients with acute PE is mandatory for determining the appropriate therapeutic management approach. Initial risk stratification is based on clinical symptoms and signs of haemodynamic instability, which indicate a high risk of early death.\textsuperscript{16} If untreated the risk of death from PE is high. If treated with heparin and oral anticoagulants, the risk of death is considerably lower.\textsuperscript{17}

Other complications of PE include:

- acute bleeding during treatment, this is more of a risk in those over the age of 65 and a particular risk for those over 75
- pulmonary infarction, when blood flow to lung tissue is disrupted this can lead to tissue death
- cardiac arrest due to ventricular collapse as a result of massive PE, although this occurs in less than 5 percent of patients, it is linked to a mortality rate is 65 to 90 percent
- chronic thromboembolic pulmonary hypertension, a condition where chronic pulmonary blood clots elevate pulmonary blood pressure which can lead to heart failure, this occurs in 1.5 to 3.8 percent of people following an acute PE
- recurrent venous thromboembolism (VTE).\textsuperscript{18}

Section 5.6 \textit{Prognostic assessment strategy} of the 2019 ESC \textit{Guidelines on Acute Pulmonary Embolism (Diagnosis and management of)} gives details about the prognosis for those with PE. Additionally, Section 7. \textit{Chronic thromboembolic pulmonary hypertension} offers more detail about this complication of PE.
Management
The initial management of suspected PE in primary care is outlined in the NICE CKS *Pulmonary embolism, Scenario: Managing suspected pulmonary embolism*, which covers the assessment of the clinical probability of pulmonary embolism and other primary care management of people with suspected pulmonary embolism, and briefly covers investigations that may be carried out in secondary care to confirm or exclude the diagnosis.¹⁹ Note: the October 2020 update of this CKS included a contraindication (severe allergic reaction) of dalteparin in line with the manufacturer’s revised *Summary of Product Characteristics*. Diagnosis of PE is confirmed and treatment started in secondary care.

Therapeutic options
Depending on the reason for thrombosis, there are several oral therapies now available for treatment of PE, including warfarin²⁰ and the direct-acting oral anticoagulants (DOACS):

- **rivaroxaban** – is recommended as an option for treating pulmonary embolism and preventing recurrent deep vein thrombosis and pulmonary embolism in adults.²¹
- **edoxaban** – is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.²²
- **apixaban** – is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.²³
- **dabigatran** – is recommended, within its marketing authorisation, as an option for treating and for preventing recurrent deep vein thrombosis and pulmonary embolism in adults.²⁴

More information about DOACs can be found by accessing *NICE’s technology appraisals* or the individual monographs via the *electronic Medicines Compendium (eMC)*.

Some important notes:
- **Rivaroxaban**: Rivaroxaban should be taken orally with food. The recommended dose of rivaroxaban for the treatment of pulmonary embolism is 15 mg twice daily (on days 1–21), followed by a maintenance dose of 20 mg once daily.
- **Dabigatran**: The recommended oral dose of dabigatran for the treatment of pulmonary embolism (following treatment with a parenteral anticoagulant for at least five days) is:
  - 150 mg twice daily in people aged 18–74 years
  - 110 to 150 mg twice daily in people aged 75–79 years
  - 110 mg twice daily in people aged 80 years and over.
- **Edoxaban**: The recommended oral dose of edoxaban for the treatment of pulmonary embolism is 60 mg once daily (30 mg once daily in people, with body weight of 61 kg or less) following initial use of parenteral anticoagulant for at least five days.
- **Apixaban**: The recommended oral dose of apixaban for the treatment of pulmonary embolism is 10 mg twice daily for seven days, followed by a maintenance dose of 5 mg twice daily.
- **Warfarin**: Warfarin should be started within 24 hours of confirmed pulmonary embolism and is taken orally in combination with a parenteral anticoagulant — low molecular weight heparin (LMWH). The LMWH is started as soon as possible and continued for at least five days, or until the international normalised ratio (INR) is two or above for at least 24 hours, whichever is longer, and the warfarin continued for at least three months. The typical induction dose of warfarin is 10 mg daily for two days, and the daily maintenance dose is usually 3 to 9 mg taken at the same time each day. However, doses should be tailored depending on the person’s INR.
For detailed prescribing information refer to NICE CKS topic Anticoagulation - oral.

**Initial treatment**

_Haemodynamically stable_

When PE has been confirmed in people who are haemodynamically stable, treatment is started as soon as possible with either:

- a parenteral anticoagulant (low molecular weight heparin (LMWH) or fondaparinux or with an unfractionated heparin infusion in significant renal impairment).\(^{20}\) Patients can then be considered for oral anticoagulation with warfarin (with at least five days of heparin) or a DOAC\(^ {16}\) or
- a DOAC that is licensed for the treatment of PE without the requirement for an initial treatment phase with heparin (apixaban or rivaroxaban).\(^ {16,25}\)

_Haemodynamically unstable_

People who are haemodynamically unstable may be offered thrombolytic therapy (eg, alteplase) or embolectomy (surgical removal of the embolus).\(^ {20}\)

Further information can be found in Section 5 _Treatment in the acute phase_ of the 2019 ESC Guidelines on Acute Pulmonary Embolism (Diagnosis and management of). This section also explores the bleeding risks associated with these treatments.

**Ongoing treatment**

If initial treatment is with heparin/LMWH, an oral anticoagulant is usually offered (switching to warfarin with appropriate overlap until the INR is in range, or a DOAC) and continued for at least three months.\(^ {20,16}\) People who are pregnant or have cancer are generally treated with a LMWH for a longer period\(^ {20}\) (although DOACs are starting to be offered to those with cancer).

For more information about initial treatment access the NICE CKS Pulmonary embolism, Scenario: Managing confirmed pulmonary embolism. Links to Prescribing Information for parenteral and oral anticoagulants are also included in this CKS section.

Full treatment guidance can be found in NICE guideline Venous thromboembolic diseases: diagnosis, management and thrombophilia testing [NG158] which includes a section on the information that should be offered to people with regard to anticoagulant treatment – section 1.5 Information and support for people having anticoagulation treatment.

The British Thoracic Society (BTS) Guideline for the outpatient management of pulmonary embolism offers guidance on how to risk-stratify patients with suspected and confirmed pulmonary embolism and subsequently manage them in an outpatient or ambulatory care setting.

**Prevention**

Prevention of venous thromboembolism (VTE) is a national priority. NICE guideline Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism [NG89] covers assessing and reducing the risk of VTE in people aged 16 and over in hospital.
Fact sheet
Pulmonary embolism

The NHS recommends actions to reduce pulmonary embolism risk.6

The British Lung Foundation also offers information about prevention of PE – What can I do to avoid getting a pulmonary embolism?

Patient support
The British Lung Foundation has a dedicated Pulmonary embolism page which offers information and support.

Thrombosis UK is a charity which provides information about VTE and support to those who have experienced a VTE.

The NHS has a dedicated Pulmonary embolism page.

Further resources
CPPE’s Anticoagulation gateway page contains further learning on the topic of anticoagulation.

A module on Venous thromboembolism is available via CPPE’s website as part of the e-Learning for Healthcare learning modules.

External websites
CPPE is not responsible for the content of any non-CPPE websites mentioned on this page or for the accuracy of any information to be found there. All web links were accessed on 6 May 2021.

References


