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Review Article

Managing pulmonary embolism from presentation to extended treatment

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ABSTRACT

Pulmonary embolism (PE) remains a major healthcare problem. PE presents with a variety of non-specific symptoms, and confirmation of diagnosis involves the use of clinical risk scores, scanning techniques and laboratory tests. Treatment choice is informed by the risk of sudden death, with high-risk patients recommended to receive thrombolytic therapy or thrombectomy. Patients with less severe presentations are given anticoagulant therapy, traditionally with parenteral heparins in the acute phase of treatment, transitioning to oral vitamin K antagonists (VKAs). The limitations of these agents and the introduction of non-VKA oral anticoagulants challenge this paradigm. To date, clinical studies of four non-VKA oral anticoagulants to treat acute thrombosis have been published, and rivaroxaban is now approved for treatment and prevention of PE (and deep vein thrombosis). Rivaroxaban and apixaban alone, and dabigatran and edoxaban after parenteral anticoagulant induction, were non-inferior to enoxaparin/VKA for the prevention of recurrent venous thromboembolism; the risk of major bleeding was similar with dabigatran and edoxaban and significantly reduced with rivaroxaban and apixaban. Patients with an initial PE are recommended to receive continued anticoagulation for 3 months or longer, depending on individual risk factors, and studies of non-VKA oral anticoagulants have shown a continued benefit for up to 2 years, without a significantly increased risk of major bleeding. Given that the non-VKA oral anticoagulants are given at fixed doses without the need for routine coagulation monitoring, their adoption is likely to ease the burden on both PE patients and healthcare practitioners when longer-term or extended anticoagulation is warranted.

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Abbreviations: ACC, American College of Cardiology; ACCP, American College of Chest Physicians; ASA, acetylsalicylic acid; bid, twice daily; CI, confidence interval; CrCl, creatinine clearance; CT, computed tomography; CTPA, computed tomography pulmonary angiography; CTPH, chronic thromboembolic pulmonary hypertension; CUS, compression ultrasonography; CXR, chest X-ray; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; ESC, European Society of Cardiology; HR, hazard ratio; INR, international normalised ratio; i.v, intravenous; IVC, inferior vena cava; LMWH, low molecular weight heparin; od, once daily; OAC, oral anticoagulant; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; rtPA, recombinant tissue plasminogen activator; RR, relative risk; RV, right ventricular; s.c, subcutaneous; UFH, unfractionated heparin; V/Q, ventilation-perfusion scintigraphy; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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Introduction

Pulmonary embolism (PE) remains a significant cause of morbidity and mortality, occurring at an estimated 95 cases per 100,000 patient-years and causing over 300,000 deaths annually in Europe alone; most of these cases are undiagnosed and, therefore, untreated [1]. Chronic thromboembolic pulmonary hypertension (CTPH) is a relatively uncommon but serious complication of PE. Although the incidence of CTPH among patients with PE in contemporary studies is in the order of 0.5–1.5% [2–4], one study found that 3.8% of patients with acute PE developed CTPH within 2 years, with a 5-year mortality rate of approximately 20% [5]. Non-fatal PE may also be associated with post-thrombotic syndrome, particularly when accompanied by deep vein thrombosis (DVT) [6], and this has a substantial effect on quality of life [7].

Although traditional anticoagulants are effective for the treatment and prevention of PE, practical challenges associated with their use have led to the development of non-vitamin K antagonist (VKA) oral anticoagulants (OACs). This and the publication of the latest American College of Chest Physicians (ACCP) guidelines [8] have significantly increased the depth of knowledge required of clinicians treating PE. Here, we aim to highlight the current standard of care in the diagnosis and treatment of this difficult disorder. We focus on common practical challenges such as risk stratification, choice of initial treatment and duration of anticoagulation, with particular reference to the non-VKA OACs.

Presentation and Diagnosis of Primary Pulmonary Embolism

There are five commonly recognised ways in which PE may present:

1. Sudden death
   The 1-day survival rate after PE (64%) is much lower than after DVT (97%), and the 7-day survival rate is also poor (59%) [9]. A non-specific clinical presentation [10] means that a definite diagnosis is often established only at autopsy in patients who die of PE [11].
2. Typical clinical presentation
   In line with previous observations [12,13], a recent Italian survey found that the most common clinical symptoms of PE were dyspnoea (78–81%), pleuritic chest pain (39–56%) and fainting or syncope (22–26%) [14]. These are present individually or in combination in 90% of confirmed cases [10]. Isolated rapid-onset dyspnoea is usually attributable to the haemodynamic consequences of central PE. Pleuritic chest pain is frequent and results from pleural irritation, in which proximal or distal emboli cause pulmonary infarction and alveolar haemorrhage, sometimes with haemoptysis. Syncope, indicative of a severely reduced haemodynamic reserve and, in the most severe cases, shock and arterial hypotension, can also be present [10].
   Clinical signs of PE lack sensitivity and specificity. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study found that tachypnoea (≥20 breaths/min) and tachycardia (>100 beats/min) were significantly more common in confirmed PE than in cases where PE was excluded (57% vs. 47% and 26% vs. 16%, respectively; $P<0.01$) [15], whereas PIOPED I and another study found only small differences [12,13]. All of these studies found signs of DVT in more patients with confirmed PE than in those without PE (47% vs. 23% with calf or thigh involvement in PIOPED II; $P<0.001$) [12,13,15].
3. Atypical clinical presentation
   Cough, substernal and pleuritic chest pain, haemoptysis and wheezing occurred in up to 59% of confirmed PE cases in PIOPED I, PIOPED II and another study [12,13,15]. However, these were also common in many cases for which PE was excluded. Cyanosis and fever (>38.5 °C) were also found in only 11% and 7%, respectively, of patients with confirmed PE [13,15].
4. Asymptomatic presentation on scanning
   Asymptomatic and previously unsuspected PE are increasingly being detected in a variety of patients, as a result of the wider use and greater sensitivity of scanning techniques [16]. This is notably the case in patients with chronic lung disease and in those with cancer, partly owing to greater use of computed tomography (CT) in oncological staging [17]. CT scans found asymptomatic venous thromboembolism (VTE) in 6.3% of patients with cancer, of which 3.3% of cases were PE [18]. However, this may not translate to daily practice, because these scans were subject to careful re-assessment. A retrospective analysis of 1466 consecutive staging CT scans showed asymptomatic VTE in 2.5% of patients with cancer (95% confidence interval [CI] 1.60–3.80). This included 1.3% of patients with incidental PE or thrombosis of the inferior vena cava (IVC), iliac vein or femoral veins (95% CI 0.70–2.30) and 1.1% with abdominal vein thrombosis [19].
5. Asymptomatic presentation in association with DVT
   Routine screening of patients with symptomatic, proven DVT demonstrated an unexpectedly high proportion (51%) with probable asymptomatic PE detected by ventilation-perfusion scintigraphy (V/Q) scan [20]. In the international Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry, 35% of the 2375 patients with a proximal lower-limb DVT had asymptomatic PE [21].

Diagnosis of Patients with Pulmonary Embolism

PE is potentially fatal. Clinical severity depends on factors such as baseline cardiopulmonary reserve, embolus size and the degree to which the pulmonary circulation is occluded [22,23]. However, defining PE by these terms does not accurately describe the risk of death [23]; therefore, risk scales that allow a rapid determination of the likelihood of mortality in the period immediately after a PE are considered more clinically useful [10,23].

Initial Diagnostic Stratification Based on Mortality Risk

The 2008 European Society of Cardiology (ESC) guidelines for the management of PE refer to high-risk and non-high-risk PE. High-risk patients have a >15% mortality rate during the first 30 days after a PE (during initial in-hospital or outpatient care), whereas non-high-risk patients are further stratified as having an intermediate (3–15%) or low (<1%) mortality risk [10]. Stratification is based on the presence or absence of shock and/or hypotension, right ventricular (RV) dysfunction and myocardial injury (Table 1). Risk stratification should be done before confirmatory diagnostic tests, as shown in Fig. 1. This diagnostic pathway is described below, together with other potentially applicable diagnostic techniques.

Confirmatory Diagnostic Testing in High-risk Patients

High-risk patients have shock and/or hypotension, and have a >15% risk of early death [10]. CT pulmonary angiography (CTPA) should be

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