Improving long-term outcomes following acute pulmonary embolism

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Acute pulmonary embolism (PE) can result in complications many years after the initial event. An understanding of the long-term outcomes in patients following a PE is important to improve their management.

Key points

- **Pulmonary embolism (PE) has been thought of as an acute condition with few long-term sequelae; however, data from recent studies have revealed an effect on mortality many years after the original insult.**
- **Patients who experience an episode of PE are predisposed to later venous thromboembolic (VTE) events: VTE provoked by cancer is likely to have the highest recurrence rate, whereas VTE after surgery has the lowest recurrence rate.**
- **GPs have a vital role in the intermediate- to long-term anticoagulation management of patients who have had a PE.**
- **Chronic thromboembolic pulmonary hypertension should be considered in patients with previous PE or VTE who present with ongoing or unexplained dyspnoea, exercise intolerance, atypical chest pain, syncope or peripheral oedema.**
- **There is increasing evidence of persistent functional and right ventricular impairment among long-term survivors of submassive PE.**
- **Patients who have had a PE have been found to have a threefold increase in 30-year mortality compared with controls, even after adjustment for comorbidities.**

CARDIOLOGY TODAY 2016; 6(2): 25-28

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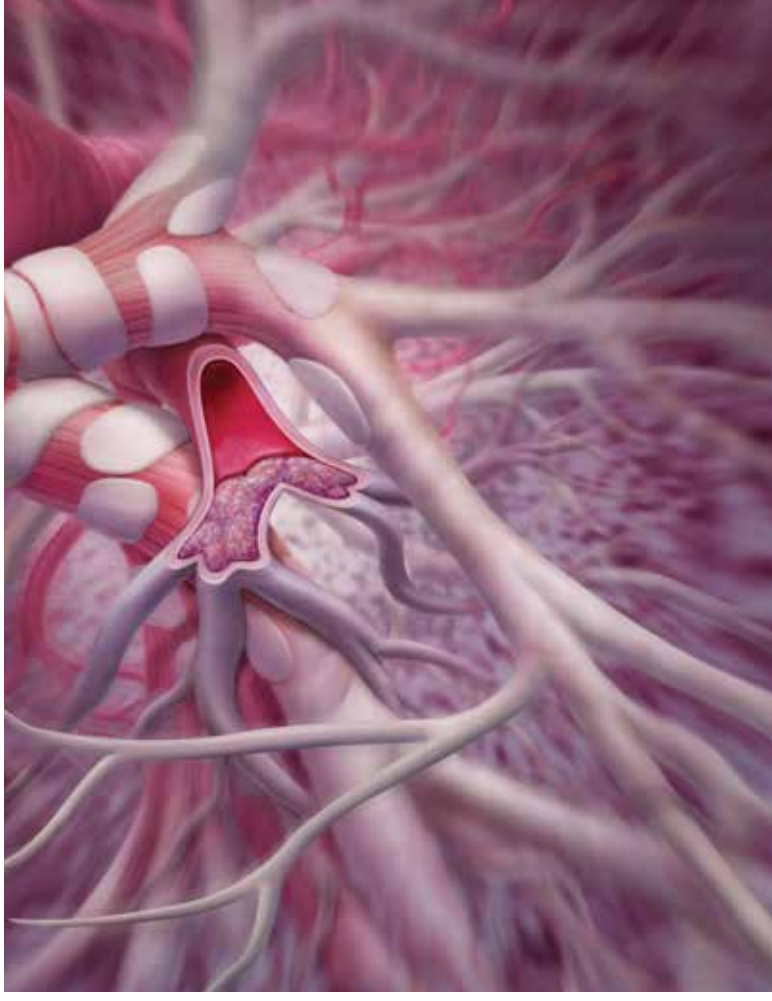


Pulmonary embolism (PE) is a common and severe manifestation of venous thromboembolic (VTE) disease, with an annual incidence estimated at 0.3 cases per 1000 persons in Australia.[1] The short-term mortality after acute PE ranges from 9 to 17% at three months post-diagnosis,[2-4] which is comparable with that of an ST-elevation myocardial infarction (MI) over the same period.[5] Unlike MI, however, the age-standardised mortality rates from PE has not improved as significantly over the last decade and there are no guidelines for long-term follow up of patients who have had a PE.[6]

Traditionally, PE has been thought of as an acute condition with few long-term sequelae. However, data from more recent studies have revealed an effect on mortality many years after the original insult.[7,8] This review summarises the effects of PE on long-term morbidity and mortality and its management.

Long-term morbidity

Recurrent pulmonary embolism

Patients who experience an episode of PE are predisposed to later VTE events. In a long-term observational study of 2218 patients with their first VTE event, the cumulative incidence of recurrent VTE was found to be 6% at one year and 18% at 10 years, suggesting that the risk of recurrence continues for an extended period of time.[9] Furthermore, the risk of recurrent VTE is heavily influenced by the presence and nature of the provoking factor. Unprovoked VTE has a very high recurrence rate, estimated at approximately 10% at one year and 30% after five years, whereas VTE after surgery has the lowest recurrence rate, at 1% at one year and 3% after five years.[10]

Table 1. Dosing regimen for PE treatment using DOACs PBS listed for this indication*

DOAC	Dose	Important contraindications
Apixaban	10 mg twice daily for 7 days; followed by 5 mg twice daily for 6 months for acute treatment of PE; followed by 2.5 mg twice daily thereafter to prevent recurrence	Severe renal impairment (CrCl <25 mL/min) Severe hepatic impairment Concomitant treatment with CYP3A4 and P-glycoprotein inhibitors
Rivaroxaban	15 mg twice daily for 3 weeks; followed by 20 mg once daily thereafter	Severe renal impairment (CrCl <30 mL/min) Moderate to severe hepatic impairment Concomitant treatment with CYP3A4 and P-glycoprotein inhibitors

* Refer to each medication's approved product information for full prescribing details (dabigatran is currently not PBS-listed for the treatment of acute VTE).
Abbreviations: CrCl = creatinine clearance; DOACs = direct oral anticoagulants; PBS = Pharmacuetical Benefit Scheme; PE = pulmonary embolism.

VTE provoked by cancer probably has the highest recurrence rate (estimated at 15% at one year); however, long-term recurrence rates in this subgroup are not known due to high short-term mortality rates.[10]

Duration of anticoagulation treatment

Selecting an optimal duration of anticoagulation treatment is important in preventing recurrent PE. Both the American College of Chest Physicians (ACCP) and European Society of Cardiology (ESC) guidelines make similar recommendations for the following groups of patients:

- for patients with provoked PE (excluding malignancy), three months of anticoagulation
- for patients with PE in the setting of active malignancy, indefinite anticoagulation
- for patients with unprovoked PE, a risk–benefit assessment at three months following the event, with indefinite anticoagulation for those at low to moderate risk of bleeding and discontinuation for patients at high risk of bleeding.[10,11]

Importantly, these recommendations place a heavy emphasis on reducing recurrent PE at the cost of increasing bleeding events. Therefore, formal discussions with patients about their expectations and preferences are vital before embarking on a strategy of indefinite anticoagulation. The decision to continue or stop indefinite anticoagulation should also be revisited regularly as patient clinical status and bleeding risk are likely to change over time.

Choice of anticoagulation treatment

Warfarin has traditionally been the agent of choice for patients requiring indefinite anticoagulation, resulting in a 95% reduction in recurrent PE rates when compared with placebo.[12] With the advent of direct-acting oral anticoagulants (DOACs), clinicians now have a multitude of options to choose from when considering long-term anticoagulation. Dabigatran, rivaroxaban and apixaban have all been shown in randomised controlled trials to reduce recurrent VTE by approximately 80 to 90%.[13-15] Furthermore, patients on dabigatran have been found to have significantly lower rates of major or clinically relevant bleeding when compared with warfarin.[13] Currently only the factor Xa inhibitors rivaroxaban and apixaban are approved under the Pharmaceutical Benefits Scheme for the treatment of VTE in Australia. The use of aspirin after the minimum duration of anticoagulation has also been shown to reduce the rate of recurrent VTE by approximately 45% with no apparent increase in major bleeding.[16] The 2014 ESC guidelines have subsequently been updated to recommend consideration of DOACs as an alternative to warfarin for indefinite anticoagulation, and consideration of the long-term use of aspirin for patients who refuse or are unable to tolerate oral anticoagulants after the minimum time period of anticoagulation is completed.[11]

Role of the GP

The GP has a vital role in the intermediate to long-term anticoagulation management of patients who have had a PE. The decision to use warfarin or a DOAC will be influenced by the GP's experience, patient preference, ease of monitoring and comorbidities (such as chronic kidney disease) that may impact on the pharmacokinetics of these agents. For a patient with unprovoked PE, the GP can provide counselling on the risks and benefits of indefinite anticoagulation, guiding the patient to a rational decision after a thorough discussion of their expectations. Also, the long-term relationship between the GP and patient allows the GP to assess indefinite anticoagulation strategies at regular intervals, encourage patient adherence to therapy, and make any necessary adjustments in the event of a change in patient clinical status.

A brief summary of the dosing regimens and important contraindications of DOACs in the treatment of PE is provided in Table 1.

Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a devastating long-term complication of PE, associated with high morbidity and mortality if left untreated. Registry data show that 75% of all patients with CTEPH had a past clinical history of PE.[17] The pathophysiology of CTEPH remains incompletely understood but it has multiple components beginning with incomplete thrombus resolution, subsequent inflammation and eventual remodelling of the proximal large vessels and distal small vessels in the pulmonary arterial circulation.[18-20] Prospective observational studies have found CTEPH to have a cumulative incidence of 1 to 4% two years after acute PE.[21,22] The true incidence of CTEPH post-PE is likely to be underestimated in these studies

as additional cases may arise from asymptomatic VTE events.[23]

Signs, symptoms and investigations

The symptoms and signs of CTEPH are non-specific, and diagnosing the condition requires a high degree of suspicion. Registry data from European referral centres show the median delay from symptoms to diagnosis to be approximately 14 months.[17] Dyspnoea is almost invariably present and other symptoms include oedema, fatigue, chest pain and syncope. Physical examination can be normal or reflect underlying pulmonary hypertension. Important signs include right parasternal heave, loud P2 and signs of right ventricular failure.[24]

In a patient with symptoms suspicious of CTEPH, the initial workup should include a transthoracic echocardiogram (TTE) and pulmonary ventilation/perfusion (VQ) scan (Figures 1 and 2).[25] TTE provides a non-invasive estimate of the pulmonary arterial pressure, and the VQ scan allows visualisation of perfusion defects. Unlike for acute PE, VQ scanning is preferred over computed-tomography (CT) pulmonary angiography as the initial test for diagnosis of CTEPH due to superior sensitivity and reduced radiation exposure.[25] Where possible, patients should be referred to an expert pulmonary hypertension centre to confirm the diagnosis in the event of abnormal screening tests or if there is an ongoing high degree of suspicion.

Treatment of CTEPH

The gold standard treatment for CTEPH is surgical pulmonary endarterectomy, which, when performed in specialised multidisciplinary centres, leads to significantly improved symptoms and haemodynamics but has an operative mortality of 5%.[26] For patients who are ineligible or considered too high risk for surgery, targeted medical therapy such as with the novel soluble guanylate cyclase stimulator riociguat has emerged as a viable treatment, with studies showing significant improvements in patients' exercise capacity and pulmonary vascular resistance.[27] Balloon pulmonary angioplasty may also be an alternative option in specialised centres, with studies showing improvements in pulmonary pressures and symptoms after the procedure.[28]

Role of the GP

Identification of CTEPH as a cause of pulmonary hypertension is important as it may be a potentially curable condition. Even though it is uncommon, GPs should consider CTEPH in patients with previous PE or VTE who present with ongoing or unexplained dyspnoea, exercise intolerance, atypical chest pain, syncope, or peripheral oedema. Routine screening for asymptomatic patients after a PE, however, is not supported by current guidelines.[29]

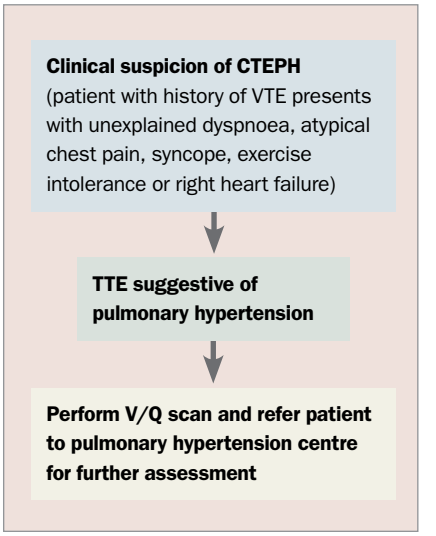
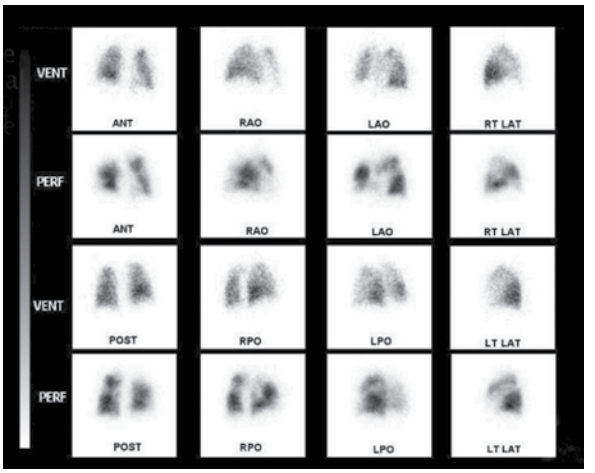
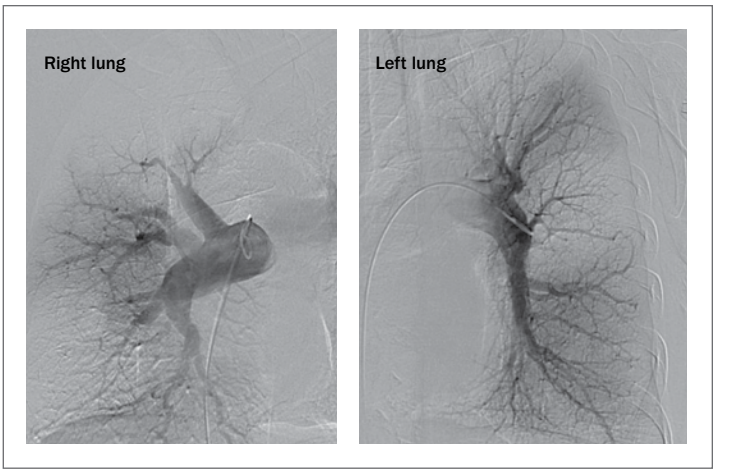


Figure 1. Simplified steps for screening patients for chronic thromboembolic pulmonary hypertension.
Abbreviations: CTEPH = chronic thromboembolic pulmonary hypertension, TTE = transthoracic echocardiogram, V/Q = ventilation/perfusion, VTE = venous thromboembolism.

Functional impairment after pulmonary embolism

Although most patients do not develop CTEPH, there is increasing evidence of persistent functional and right ventricular impairment among long-term survivors of submassive PE.[30-33] A reduction in exercise capacity was observed on six-minute walk test in up to 16% of long-term survivors of submassive PE when compared with age- and





Figures 2a and b. Imaging studies of a patient with chronic thromboembolic pulmonary hypertension. (a, left). Pulmonary ventilation–perfusion (VQ) scan showing extensive multiple, bilateral, segmental, mismatched, perfusion defects. (b, right). Pulmonary angiogram. In the right lung there is marked attenuation of the subsegmental branches, with significant difference in size of vessels suggestive of recanalised vessels. There is reduced perfusion throughout the right lung in keeping with chronic pulmonary embolism. Similar changes are seen in the left lung.

Table 2. Mortality outcomes for patients with different chronic cardiovascular diseases

Cohort	Mortality outcome	Recommended long-term follow up
Patients with chronic heart failure[43]	Annual rate = 10.9%[43]	3 to 6-monthly review
Outpatients with stable coronary artery disease[44]	Annual rate = 1.4%	4 to 12-monthly review
Patients with ST-elevation myocardial infarction[45]	1-year cumulative rate = 8.0%	4 to 12-monthly review
Patients with pulmonary embolism[7]	1-year cumulative rate = 16.3% Annual rate = 8.5%	Annual review for patients on extended anticoagulant therapy*

* Updated recommendation[42] based on the *Antithrombotic Therapy and Prevention of Thrombosis, 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines*.[46] For patients who complete a finite duration of anticoagulation therapy following acute PE, there is currently no follow-up recommendation.

sex-matched controls without PE.[33] On echocardiography, persistent mild pulmonary hypertension and right ventricular dysfunction were noted in 29% and 13% of survivors, respectively, and was associated with elevation in N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin-T levels, independent of coexisting comorbidities.[33] Therefore, there should also be an increased awareness and screening of patients of these previously unrecognised long-term consequences of submassive PE.

Malignancy screening

Malignancy is a known precipitating factor of PE; however, opinions on the need for intensive cancer screening in patients after a PE remain divided. Observational studies have found a slightly increased risk of developing a new cancer after an episode of PE,[34-36] which may not justify aggressive investigation for all patients. The SOMIT (Screening for Occult Malignant disease in Idiopathic venous Thromboembolism) trial was a randomised controlled study that showed that extensive screening in patients who had had an idiopathic PE identified malignancies at an earlier stage and improved the mean delay to diagnosis by 10 months. However, the prognostic benefit of this early detection remains uncertain as the study was not adequately powered to examine for difference in mortality.[37] A separate cost analysis of the SOMIT study data showed that screening with CT scanning of the abdomen combined with sputum cytology and mammography has the potential to be cost-effective given its acceptable sensitivity and specificity.[38] A more recent prospective cohort study comparing baseline screening (consisting of history, physical examination, basic laboratory tests and chest x-ray) with extensive screening (addition of mammography and CT scanning of chest and abdomen) found no mortality benefit in the latter group.[39]

Given the lack of definitive evidence in this area, major society guidelines have not made firm recommendations regarding the issue of malignancy screening in PE. Until more evidence arises, current practice should include at least a comprehensive history, physical examination and basic laboratory tests to search for clues of an underlying malignancy. As most malignancies are found within the first year after a PE, more frequent follow up by GPs during this critical period may help in diagnosing an underlying cancer earlier.

Long-term mortality

Most contemporary observational studies have evaluated short-term (defined as three months or less) outcomes post-PE, with only a small number of studies evaluating long-term outcomes. Our own single-centre study of 1023 patients post-PE found a five-year cumulative mortality rate of 32%.[7] In this group of patients, cardiovascular disease (31%) was the most common cause of death after discharge, followed by malignancy (27%) and sepsis (21%), with recurrent PE accounting for only 5% of deaths. The largest study to date, from the Danish National Registry of Patients, compared 54,066 patients with PE with age and sex-matched controls without PE. Patients who had had a PE were found to have a threefold increase in 30-year mortality compared with controls, even after adjustments for differences in comorbidities.[8] Furthermore, the leading cause of long-term deaths in this study was related to diseases of the circulatory system. The mechanism behind the high proportion of cardiovascular deaths has not been elucidated but persistent hypercoagulability and high prevalence of atherosclerotic risk factors in patients who have had a PE may be contributors.[40,41]

Despite unfavourable long-term mortality compared with patients with other chronic cardiovascular diseases, current guidelines do not offer long-term follow-up recommendations in patients post-PE except for those on extended anticoagulation therapy (Table 2).[42] Until more evidence becomes available, the search for underlying cardiovascular disease and malignancy in patients with PE should be considered on a case-by-case basis.

Summary

PE is associated with significant long-term morbidity and mortality. GPs have an important role in initial suspicion of PE and in the long-term follow up of patients to monitor for the development of complications. **CT**

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A list of references is included in the website version of this article (www.cardiologytoday.com.au).

COMPETING INTERESTS: Dr Wong, Dr Chow and Dr Ng: None. Professor Kritharides has received grants and/or consultancy fees from Amgen, AstraZeneca and Merck Sharp and Dohme.

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