J R Coll Physicians Edinb 2009; 39:107–12

The diagnosis and treatment of acute pulmonary thromboembolism

[1]TN Martin, [2]AJB Brady*
[1]Specialist Registrar Cardiology/General Internal Medicine, Golden Jubilee National Hospital, Beardmore Street, Clydebank;
[2]Consultant Cardiologist, Department of Medical Cardiology, Glasgow Royal Infirmary, Glasgow, UK

ABSTRACT Acute pulmonary embolism is a common major medical condition and is frequently poorly managed. There has been wide variation within and between countries, and even within hospitals, on how to diagnose and treat this frequently encountered medical emergency. This review examines the current status and advances now available in most acute centres, and reveals how the new European Society of Cardiology guidelines simplify this complex and poorly understood condition. Particular emphasis is placed on the new role of biochemical markers of myocardial stress and on the definition of right ventricular dysfunction as key determinants of severity and risk of death and for specific therapy.

KEYWORDS European Society of Cardiology guidelines, pulmonary thromboembolism

DECLARATION OF INTERESTS No conflict of interests declared.

*Writing committee, European Society of Cardiology PTE guidelines committee; British Thoracic Society PTE guidelines committee; SIGN PTE guideline committee

Published online ***March 2009***

Correspondence to ***AJB Brady, Department of Medical Cardiology, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, UK***

tel. ***+44 (0)141 211 4727***
fax. ***+44 (0)141 211 1171***
e-mail ***a.j.brady@clinmed.gla.ac.uk***

A diagnosis is easy as long as you think of it.
– Soma Weiss (1899–1942), US physician

INTRODUCTION

There are certain conditions that prompt urgent investigation as soon as they enter the differential diagnosis. Pulmonary thromboembolism (PE) is among the most important, with an in-hospital mortality rate of 6–15% and a high proportion of early deaths.[1,2] Indeed, this mortality rate is higher than the inpatient mortality for myocardial infarction. Yet PE is often missed, and frequently poorly managed. If PE is suspected in primary care then the patient should be rapidly sent to the nearest appropriate secondary care service for diagnosis and appropriate treatment.[3]

The annual incidence of PE is 23–69 cases per 100,000, and increases with age.[4,5] In half of these cases it is the primary complaint; the remainder occur while the patient is under hospital care for another reason. Overall, three-quarters of patients will have a recognised predisposing factor (Table 1).

This article focuses on suspected PE and only deals with deep venous thrombosis (DVT) where relevant, although they are both part of the spectrum of venous thromboembolism (VTE). The European Society of Cardiology (ESC) published its new PE guidelines in September 2008.[3] Much of the present article takes cognisance of this highly detailed contemporary statement from the ESC. There has been considerable progress since the publication of the existing UK guideline, the British Thoracic Society (BTS) guidance of 2003. The BTS has begun a complete revision of this guideline and plans to publish it in late 2009 or 2010. The Scottish Intercollegiate Guidelines Network (SIGN) has begun work on its first specific guideline for this critical condition.

TABLE 1 Major and minor risk factors for venous thromboembolism

Major risk factors (relative risk 5–20)	Minor risk factors (relative risk 2–4)
Surgery	Cardiovascular
Obstetrics	Oestrogens
Lower limb problems	Chronic illness
Malignancy	Travel
Reduced mobility	
Past history of proven VTE	

Adapted from the British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003; 58: 470–83.

DIAGNOSTIC APPROACH

There has been a lack of precision in terminology regarding the diagnosis and management of PE in general hospital practice. The BTS 2003 guideline was produced to clarify this and the 2008 ESC guidance attempts to further refine these issues. There are two principal areas of confusion. The first is the definition of the likelihood, or probability, of the clinical features and baseline tests being those of a pulmonary embolus. The second is the

TABLE 2 Wells score

Variables	Points
Predisposing factors	
Previous PE or DVT	+1.5
Recent surgery or immobilisation	+1.5
Cancer	+1
Symptoms	
Haemoptysis	+1
Clinical signs	
Heart rate >100 beats per minute	+1.5
Clinical signs of DVT	+3
Clinical judgement	
Alternative diagnosis less likely than PE	+3
Clinical probability (3-level)	**Total**
Low	0–1
Intermediate	2–6
High	≥7

TABLE 3 Revised Geneva score

Variables	Points
Predisposing factors	
Age >65 years	+1
Previous DVT or PE	+3
Surgery or fracture within one month	+2
Active malignancy	+2
Symptoms	
Unilateral lower limb pain	+3
Haemoptysis	+2
Clinical signs	
Heart rate	
75–94 beats per minute	+3
≥95 beats per minute	+5
Pain on lower limb deep vein at palpation and unilateral oedema	+4
Clinical probability (3-level)	**Total**
Low	0–3
Intermediate	4–10
High	≥11

determination of severity, or risk of death, from the PE. Confusion exists when 'risk' and 'probability' are used interchangeably. In this review we hope to make clear the appropriate terminology.

There are many ways in which a PE may present, ranging from dyspnoea and/or pleuritic chest pain to haemodynamic collapse. History and examination are unreliable, particularly in excluding the diagnosis of PE.

Defining individual clinical probability of PE is fundamental. Patients have high probability if they have clinical features of PE, a major risk factor and an absence of a reasonable alternative explanation. Tables to define individual probability are well established but poorly used and should be referred to much more often.

The most frequently used and therefore best validated are the Wells score and the Revised Geneva score.[6–9] The Wells score includes a clinical judgement on whether an alternative diagnosis is more likely than a PE and carries significant weight, but is necessarily subjective (Table 2). The original Geneva score required an arterial blood gas analysis on air but has since been revised (with comparable predictive value) and is entirely based on clinical variables (Table 3). The two scores have been shown to have equivalent performance in ruling out PE when combined with D-dimer measurement.[10] The prevalence of PE in patients with low or intermediate probability Geneva scores is 20% as opposed to 83% when the probability is high.[11]

INVESTIGATION

The initial presentation of the individual with suspected PE defines the management strategy. The stratification is determined by clinical status, as shown in Figure 1. The patient with shock has a high mortality risk and appropriate investigations and treatment must be initiated without delay. The patient who is clinically stable should also receive treatment immediately, but imaging tests need not necessarily be performed as an emergency procedure. Figure 1 also shows the diagnostic algorithms for patients presenting with and without clinical features of shock.

Laboratory tests

For patients with a low or moderate pre-test probability of PE, D-dimer levels should be assessed using a highly sensitive enzyme-linked immunosorbent assay (e.g. Vidas ELISA). A negative plasma D-dimer result (<500 µg/l) in these patients does not require further investigation, with a three-month thromboembolic risk in patients left untreated below 1%.[12–18] If there is a high pre-test clinical probability then there is no need to do the test. The D-dimer test also does not need to be used in patients that are post surgery, aged over 80 years, pregnant or have cancer. The D-dimer concentrations in these groups of patients are frequently non-specifically elevated.

The widespread availability of biochemical markers of myocardial injury, most frequently troponin I or T(19) (or brain natriuretic peptide),[20] has revolutionised our understanding of risk in PE. Patients with an undetectable troponin have a very low mortality from PE; individuals with a raised troponin have a much higher mortality, especially if there is right ventricular dysfunction. This is summarised in Table 4 below.

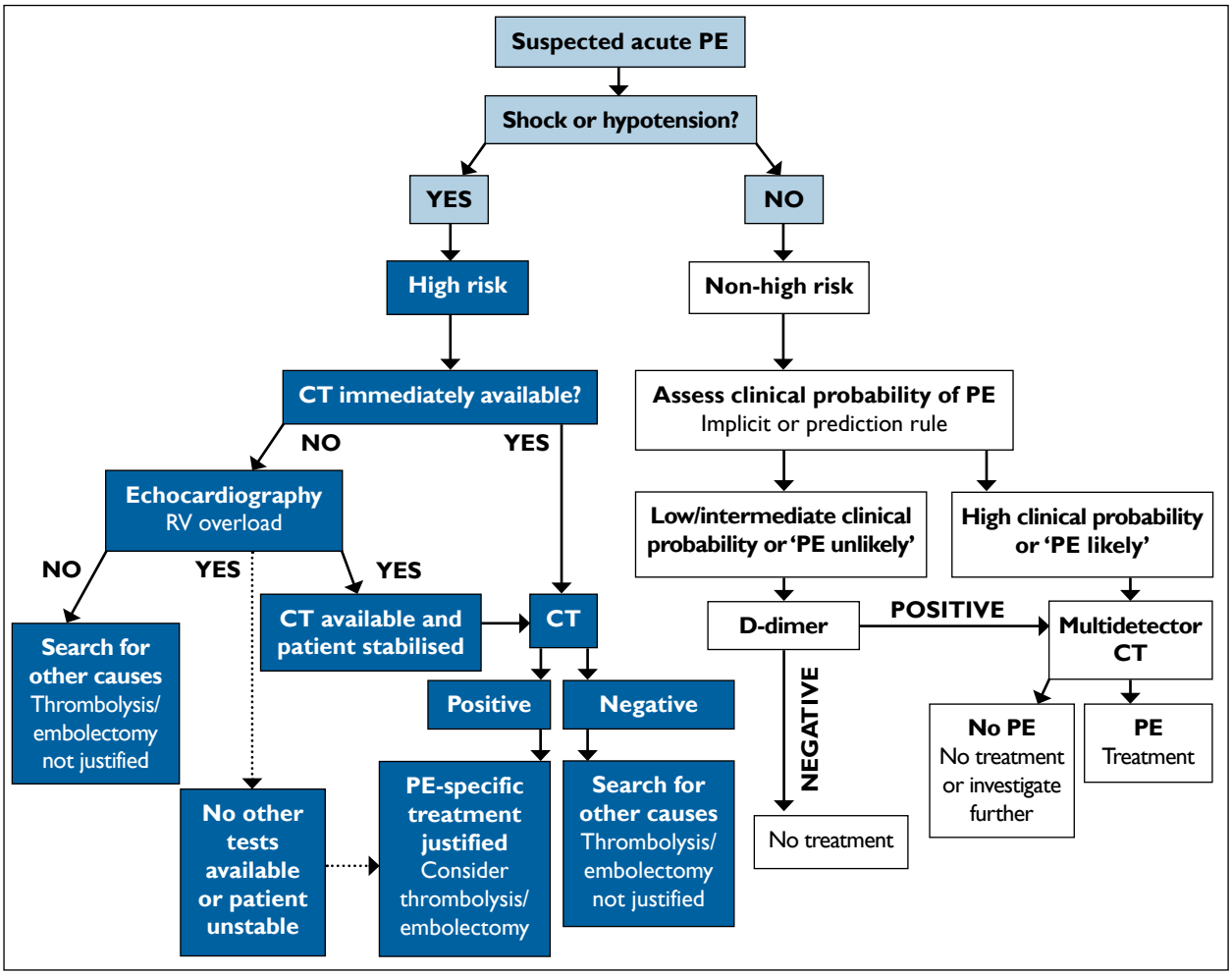

FIGURE 1 Clinical status and management strategy for suspected acute PE (adapted from the ESC guidelines).

Imaging

A chest X-ray is often taken but may be normal in PE, unless there is other pathology present. For example, later in the natural history of PE, if pulmonary infarction has occurred there may be atelectasis in subpleural areas, but this is of little value in the acute presentation. In most centres, ventilation-perfusion scintigraphy (V/Q) isotope scanning and computed tomography pulmonary angiography (CTPA) are used to make the diagnosis of PE. Computed tomography pulmonary angiography is gradually replacing isotope scanning as the investigation of choice and the combination of clinical probability, D-dimer testing and CTPA to guide management of suspected PE has been validated in prospective trials.[15,16] Computed tomography pulmonary angiography provides additional prognostic information such as the size of the right ventricle. There is still a role for isotope scanning if there are concerns regarding contrast injection, but a lung scan is generally not recommended as a single test.

Computed tomography pulmonary angiography is the best test in patients with an elevated D-dimer level and is the first-line test in patients with a high clinical probability. A negative CTPA has been shown to safely exclude PE (98.7–99.7% accuracy at three months) in several large-scale outcome studies.[11,16] An isolated subsegmental thrombus is the exception where the exclusion of DVT will help plan management.

Isotope scanning (the V/Q scan) for the detection of segmental lung ventilation perfusion mismatches (strictly ≥2) has been in use for many years. However, it only reliably diagnoses or excludes PE in patients who do not have underlying cardiac or pulmonary diseases. Further imaging is required if the probability of the V/Q scan is in the face of intermediate or high probability, or high with a low clinical probability. If the suspicion of PE is high, an urgent V/Q scan or CTPA should be performed. Out of office hours it may be easier to obtain a CTPA than a V/Q scan.

Venous compression Doppler ultrasonography to identify thrombus in lower limb veins has its advocates and should be reserved for patients with suspected PE in whom a CTPA is impossible (allergy to iodine contrast dye is only a relative contraindication in the emergency situation), or if there are concerns about radiation. Pulmonary angiography was the gold standard from the

TABLE 4 New risk stratification table from the European Society of Cardiology's 2008 guideline[3]

PE-related early mortality risk		Risk markers			Potential treatment implications
		Clinical (shock or hypotension)	RV dysfunction	Myocardial injury	
High >15%		+	(+)	(+)	Thrombolysis or embolectomy
Non-high	Intermediate 3–15%	–	+	+	Hospital admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

1960s and allows direct haemodynamic measurements to be made, but because it is invasive and because modern CTPA techniques are so good it tends to be reserved for select situations where intravascular fragmentation of massive thrombus is being considered.

ACUTE TREATMENT

All patients usually require supplemental oxygen. Immediate definitive treatment is determined by cardiovascular stability. Table 4 shows the major risk markers in the stratification of patients with a PE and serves as a guide to potential treatment implications.

Haemodynamically unstable

These patients have a PE-related mortality risk of more than 15%, it is an emergency situation and the clinical probability is usually high. Shocked patients need haemodynamic support with fluids and inotropes (noradrenaline, dobutamine or dopamine) and specific treatment strategies which include thrombolysis, surgical embolectomy or catheter disruption. Simply administering subcutaneous heparin and hoping for the best is poor medicine, and this practice must be abandoned.

Thrombolytic therapy rapidly resolves thromboembolic obstruction and exerts beneficial effects on haemodynamic parameters with more than 90% of patients classified as responders within the first 36 hours.[21] The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for six to 14 days. A meta-analysis of thrombolytic therapy versus heparin in haemodynamically unstable patients showed a significant reduction in recurrent PE or death (9.4% vs 19.0%; OR 0.45, 95% CI 0.22–0.92; number needed to treat = 10).[22] Therefore, thrombolysis should be administered to patients with PE who have a high mortality risk, unless there are absolute contraindications to its use such as active internal bleeding or recent spontaneous intracranial bleeding.

Currently, the best agent is recombinant tissue plasminogen activator (rtPA). Urokinase or streptokinase can be used if rtPA is unavailable. Tenecteplase (TNK) is not yet licensed for PE but is the thrombolytic of choice for acute myocardial infarction and the drug being studied in the ongoing major European trial (see below).

In patients with absolute contraindications to thrombolysis or in those in whom thrombolysis has failed to improve haemodynamic status, surgical embolectomy is the preferred therapy. If not immediately available, percutaneous catheter embolectomy or thrombus fragmentation may be considered.[23] Although no controlled trials are available of catheter embolectomy for acute PE, there are cohort studies that suggest outcomes are similar to surgery.[24]

Pending the decision to thrombolyse or perform embolectomy by thoracotomy or percutaneously, full dose, weight-adjusted intravenous heparin should be administered immediately upon clinical diagnosis while the decision for specific therapy is being considered. Subcutaneous low molecular weight heparin (LMWH) is poorly absorbed from underperfused skin in shocked patients and should not be used.

Chronic pulmonary hypertension is a recognised long-term complication of pulmonary embolism and is associated with considerable morbidity and mortality.[25] The cumulative incidence of chronic thromboembolic hypertension (CTPH) post PE has been shown prospectively to be about 4% at two years, with no new cases occurring after this time point.[26] Potential risk factors include multiple episodes of pulmonary embolism, a larger perfusion defect, a younger age and idiopathic presentation of pulmonary embolism. The use of thrombolytic treatment was related in the univariate model to an increased risk of CTPH but not after adjustment for other risk factors and was likely due to extensive PE at presentation.

Haemodynamically stable

Most patients fall into this category. There is the greatest body of evidence for these individuals, and patients who are non-high risk usually have a favourable prognosis. There is currently no evidence to support the use of thrombolysis in unselected patients with PE.[22] Patients at intermediate risk of death (normotensive but with evidence of right ventricular strain or damage) may have a risk–benefit ratio that favours thrombolysis, particularly without an elevated bleeding risk. A large multinational European trial has been initiated and will attempt to resolve the controversy still surrounding the appropriate treatment of this group of patients (ClinicalTrials.gov number NCT00639743).

Until the results of this trial are available, standard management is anticoagulation with weight-adjusted LMWH using either enoxaparin 1 mg/kg twice daily or tinzaparin 175 IU/kg once daily while awaiting results of diagnostic work-up. Low molecular weight heparin should be given with care in patients with renal failure and the dose adjusted according to anti-Xa level.

Warfarin should be given as soon as possible and preferably on the same day as the initial anticoagulant. Heparin should be stopped when the international normalised ratio (INR) lies between 2.0 and 3.0 for at least two consecutive days. Patients with proximal deep vein thrombosis should be fitted with compression stockings as these have been shown to reduce the cumulative incidence of post-thrombotic syndrome in such patients at two years after the index event.

LONG-TERM TREATMENT

The aim of long-term anticoagulant treatment of patients with PE is to prevent fatal and non-fatal recurrent VTE events. Warfarin is used in the vast majority of the patients, while LMWH may be an effective and safe alternative in cancer patients.[27–29] For patients with PE secondary to a transient (reversible) risk factor such as surgery, trauma, medical illness, oestrogen therapy or pregnancy, treatment with warfarin for three months is usually enough.[30,31]

For patients with unprovoked PE, treatment with warfarin is recommended for at least three months.[32] If patients are at low bleeding risk and stable anticoagulation can be achieved, long-term oral anticoagulation may be considered. For patients with a second episode of unprovoked PE, longer treatment is recommended, but as yet there have been no trials exploring the optimum duration in such patients. Those receiving long-term anticoagulant treatment should be reassessed at regular intervals regarding the risk–benefit ratio of continuing such treatment.

Permanent inferior vena cava filters may be used when there are absolute contraindications to anticoagulation and a high risk of VTE recurrence, but these have inherent risk so their routine use is not recommended.[3]

There are a number of special situations where the diagnostic and treatment strategies may need to be specifically adjusted. Further details are not provided here, but examples include pregnancy, malignancy, right heart thrombi, heparin-induced thrombocytopaenia, chronic thromboembolic pulmonary hypertension and non-thrombotic pulmonary embolism. Thrombophilia screening is also not covered as it does not help in the acute diagnosis nor would it affect management. These topics are well covered in the 2008 ESC guideline.[3]

In a recent survey, failure to comply with evidence-based diagnostic strategies when withholding anticoagulation despite clinical suspicion of PE was related to a significant increase in the number of VTE episodes and in sudden death in the three-month follow-up.[33]

CONCLUSION

Pulmonary embolism has remained for years one of the most difficult to manage common major life-threatening conditions. In-hospital mortality exceeds that of acute myocardial infarction, yet a consensus on diagnostic and treatment pathways has been difficult to achieve. Now, with refinement of clinical probability scores, biomarkers, CTPA and the ability to rapidly image the right ventricle, making the diagnosis of PE in most cases is relatively straightforward as long as it has been considered. The use of LMWH has been a major advance, as has the option of thrombolysis in haemodynamically unstable patients. Prevention remains a challenge, as does more specific tailoring of the duration of anticoagulation.

REFERENCES

1 Kasper W, Konstantinides S, Geibel A et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol* 1997; 30:1165–71.

2 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353:1386–9.

3 Torbicki A, Perrier A, Konstantinides S et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J* 2008; 29:2276–315.

4 Silverstein MD, Heit JA, Mohr DN et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158:585–93.

5 Anderson FA, Jr, Wheeler HB, Goldberg RJ et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991; 151:933–8.

6 Wells PS, Anderson DR, Rodger M et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000; 83:416–20.

7 Wicki J, Perneger TV, Junod AF et al. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med* 2001; 161:92–7.

8 Cate-Hoek AJ, Prins MH. Management studies using a combination of D-dimer test result and clinical probability to rule out venous thromboembolism: a systematic review. *J Thromb Haemost* 2005; 3:2465–70.

9 Le Gal G, Righini M, Roy PM et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006; 144:165–71.

10 Klok FA, Kruisman E, Spaan J et al. Comparison of the revised Geneva score with the Wells rule for assessing clinical probability of pulmonary embolism. *J Thromb Haemost* 2008; 6:40–4.

11 Righini M, Le Gal G, Aujesky D et al. Diagnosis of pulmonary

embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. *Lancet* 2008; 371:1343–52.
12 Kruip MJ, Slob MJ, Schijen JH et al. Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: a prospective management study. *Arch Intern Med* 2002; 162:1631–5.
13 Perrier A, Desmarais S, Miron MJ et al. Non-invasive diagnosis of venous thromboembolism in outpatients. *Lancet* 1999; 353:190–5.
14 Perrier A, Roy PM, Aujesky D et al. Diagnosing pulmonary embolism in outpatients with clinical assessment, D-dimer measurement, venous ultrasound, and helical computed tomography: a multicenter management study. *Am J Med* 2004; 116:291–9.
15 Perrier A, Roy PM, Sanchez O et al. Multidetector-row computed tomography in suspected pulmonary embolism. *N Engl J Med* 2005; 352:1760–8.
16 Van Belle A, Buller HR, Huisman MV et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA* 2006; 295:172–9.
17 Leclercq MG, Lutisan JG, van Marwijk KM et al. Ruling out clinically suspected pulmonary embolism by assessment of clinical probability and D-dimer levels: a management study. *Thromb Haemost* 2003; 89:97–103.
18 Wells PS, Anderson DR, Rodger M et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med* 2001; 135:98–107.
19 Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007; 116:427–33.
20 Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2008; 178:425–30.
21 Meneveau N, Seronde MF, Blonde MC et al. Management of unsuccessful thrombolysis in acute massive pulmonary embolism. *Chest* 2006; 129:1043–50.
22 Wan S, Quinlan DJ, Agnelli G et al Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation* 2004; 110:744–9.
23 Brady AJ, Crake T, Oakley CM. Percutaneous catheter fragmentation and distal dispersion of proximal pulmonary embolus. *Lancet* 1991; 338:1186–9.
24 Kucher N. Catheter embolectomy for acute pulmonary embolism. *Chest* 2007; 132:657–63.
25 Fedullo PF, Auger WR, Kerr KM et al. Chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2001; 345:1465–72.
26 Pengo V, Lensing AW, Prins MH et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004; 350:2257–64.
27 Lee AY, Rickles FR, Julian JA et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. *J Clin Oncol* 2005; 23:2123–9.
28 Kakkar AK, Levine MN, Kadziola Z et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol* 2004; 22:1944–8.
29 Hull RD, Pineo GF, Brant RF et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006; 119:1062–72.
30 Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Research Committee of the British Thoracic Society. *Lancet* 1992; 340:873–6.
31 Pinede L, Ninet J, Duhaut P et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; 103:2453–60.
32 Campbell IA, Bentley DP, Prescott RJ et al. Anticoagulation for three versus six months in patients with deep vein thrombosis or pulmonary embolism, or both: randomised trial. *BMJ* 2007; 334:674.
33 Roy PM, Meyer G, Vielle B et al. Appropriateness of diagnostic management and outcomes of suspected pulmonary embolism. *Ann Intern Med* 2006; 144:157–64.