16.16 Venous thromboembolism 3711 16.16.1 Deep ven

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16.16 Venous thromboembolism CONTENTS 16.16.1 Deep venous thrombosis and pulmonary embolism 3711 Paul D. Stein, Fadi Matta, and John D. Firth 16.16.2 Therapeutic anticoagulation 3729 David Keeling 16.16.1 Deep venous thrombosis
and pulmonary embolism Paul D. Stein, Fadi Matta, and John D. Firth ESSENTIALS Deep venous thrombosis Deep venous thrombosis (DVT) is diagnosed in 1–2% of hospital- ized patients, but is often silent and is found much more frequently at autopsy. Patients typically complain of pain and/or swelling of the leg, but often the diagnosis will be considered only when the physician

detects unilateral leg swelling. Investigation—given the sinister nature of untreated DVT, it is important to confirm or refute the diagnosis with appropriate inves- tigations whenever clinical suspicion is aroused, unless the general condition of the patient makes this inappropriate. Management al- gorithms have been developed to guide strategy for investigation. These typically use scoring systems to stratify the clinical probability that the particular patient has a DVT (or pulmonary embolism). Those with a low clinical probability proceed to D-dimer testing, with further investigation not pursued if this is negative. Patients with either a high clinical probability, or a low clinical probability but elevated D-dimer, proceed to tests for the presence of thrombus in the leg veins, typically by ultrasonography. Management—a first episode of proximal DVT, diagnosed by non- invasive testing, should be treated with anticoagulation for 3 months. Longer duration of treatment may be recommended for those whose thrombosis occurred in the absence of a reversible risk factor or in those with a thrombophilic condition or cancer. For patients who do not have cancer, dabigatran, rivaroxaban, apixaban, or edoxaban are recommended over a vitamin K antagonist or low-molecular-weight heparin. Initial parenteral anticoagulation is given before dabigatran and edoxaban. If treatment is initiated with heparin (low molecular weight or unfractionated) or fondaparinux, it should be administered for ≥5 days before dabigatran and edoxaban. If a vitamin K antagonist is to be used, stop heparin or fondaparinux when the international normalized ratio is greater than 2.0 for 24 h or more. In patients with cancer, low-molecular-weight heparin is suggested over a vitamin K antagonist or novel oral anticoagulant. In patients with DVT, home treatment is recommended if home circumstances are adequate. DVT carries extensive morbidity irrespective of pulmonary embolism:
severe post-phlebitic syndrome occurs in 9% of patients by 5 years. Pulmonary embolism Acute pulmonary embolism is the third most common cardiovas- cular problem after coronary heart disease and stroke. It is a compli- cation of DVT, with emboli originating in the legs in 80% or more of cases. Immobilization, irrespective of the cause, is the most frequent predisposing factor. Common symptoms are dyspnoea (c.75%), pleuritic chest pain (c.50%), cough (c.35%), and calf or thigh pain or swelling (c.40%). Circulatory collapse (systolic blood pressure <80 mm Hg or loss of consciousness) is an uncommon (8–15%) mode of presentation in patients entered into clinical trials, but likely to be more frequent in routine clinical practice. Tachypnoea (respiratory rate 20 cycles/min or greater) is the most common physical sign (50–70%), and abnor- malities may be found on respiratory (30–50%) or cardiac (20–30%) examination. Investigation—algorithms similar to those used to guide manage- ment of patients with suspected DVT are used when pulmonary em- bolism is suspected or needs to be excluded. Patients with a low, ‘unlikely’, or moderate clinical probability and negative D-dimer are not investigated further. Patients with a high clinical probability, and those with an elevated D-dimer, proceed to tests for the presence of pulmonary emboli, typically by contrast-enhanced spiral CT, perhaps in combination with CT venous-phase imaging. Management—treatment with anticoagulants while awaiting the outcome of diagnostic tests may be appropriate, particularly if the tests cannot be obtained immediately. All patients who are hyp- oxic should be given supplementary oxygen at high concentration. Anticoagulation is as described for DVT. Thrombolytic therapy is

 not indicated as routine treatment, but is advised for those with
PE who are hypotensive or require ventilatory support, and those who deteriorate after starting anticoagulant therapy. Inferior vena cava filter—this is recommended for patients with proximal DVT or pulmonary embolism if anticoagulants are contraindicated or pulmonary embolism has

recurred while on adequate anticoagulant therapy. Administrative data show a lower in-hospital all-cause mortality with vena cava filters in patients with pulmonary embolism if they are haemodynamically un- stable (in shock or on ventilatory support) or require thrombolytic therapy or pulmonary embolectomy, and in some other patient groups, but these apparent reductions in mortality have not been investigated by randomized controlled trials. A very few survivors of acute pulmonary embolism develop chronic pulmonary thromboembolic hypertension. Treatment is pulmonary thromboendarterectomy, but only at experienced centres. Introduction Deep venous thrombosis (DVT) and pulmonary embolism (PE) are sometimes described together using the term ‘thromboembolism’. PE is a complication of DVT, with thrombi in 80% or more of cases originating in the legs. Management strategies of PE have been de- veloped that are based on the diagnosis of either PE or DVT, pro- vided the patient has good respiratory reserve. Treatment with anticoagulants is the same for both. Some physicians believe that patients can be managed better if it is known whether acute PE is present, even if a diagnosis of DVT is already established. Prognosis of untreated disease The frequency of fatal PE in patients with untreated DVT has di-minished as diagnostic tests have made it possible to diagnose DVT before it becomes extensive. In 1955, prior to the use of sensitive noninvasive tests for the early detection of DVT, the risk of fatal PE in untreated patients with clinically apparent DVT was 37%. Based on a diagnosis by radioactive fibrinogen scintiscans, the risk of fatal PE in patients with untreated DVT, most of which were subclinical, was about 5%. Early diagnosis has also reduced the risk of death from PE. In the early 1960s the mortality in untreated patients with acute PE, diagnosed on the basis of clinical features, was 26–37%, and an add- itional 36% died of recurrent PE. In 2008, the estimated case fatality rate from acute PE was 6.2%. Among patients in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) with mild PE who inadvertently escaped treatment, the mortality was 4–5%. Deep venous thrombosis Incidence and pathology In 2008, DVT was diagnosed in 1.7% of hospitalized patients aged 18 years or more in the United States of America. This represented 250 patients per 100 000 adult population. The condition is often silent: among patients with DVT detected by screening with 125I- fibrinogen scans, clinical evidence was present in 49%. Proximal DVT was found at autopsy in 22% of patients who died of various causes in a tertiary care hospital. Thrombosis of the leg veins usually occurs without inflammation. Inflammation of the walls of the veins, when it occurs, is usually secondary to the thrombosis. No clear evidence indicates that in-flammation of the veins prevents embolization, or that embolization is more frequent in those patients with thrombi not associated with venous inflammation. The valve pockets are a frequent site of origin of thrombi. Clinical features Patients may complain of pain or swelling of the leg, but physical examination remains the means by which attention is usually drawn to the potential diagnosis of DVT. DVT sometimes, but not always, leads to swelling of the leg. If restricted to the popliteal and calf veins, swelling is confined to below the knee, but if thrombosis involves the femoral and pelvic veins (or inferior vena cava), then swelling of the thigh is also expected.
A difference of circumference of the calves of 1.0 cm or more, measured 10 cm below the tibial tuberosity, is ab- normal. It is important to repeat the measurement of circumference of the calves and thighs at frequent intervals: proximal extension of a thrombus is likely to cause increased swelling. Repeated meas- urements should be made from a fixed point. It is good practice for the position of the first measurement to be marked indelibly on the patient’s skin. Homans’ sign is positive when active and/or passive dorsiflexion of the foot associated with any of the following: (1) pain, (2) incom- plete dorsiflexion (with equal pressure applied) to prevent pain, or (3) flexion of the knee to release tension in the posterior muscles with dorsiflexion. This sign was present in 44% of patients with DVT of the lower leg, and in 60% of patients with femoral venous thrombosis. The

elicitation of pain with inflation of a blood pressure cuff around the calf to 60 to 150 mm Hg has been recommended as a test for DVT. However, this test has not been shown to be more helpful than the assessment of direct tenderness or leg circumference. In one study, the sensitivity of oedema, erythema, calf tenderness, palpable cord, or Homans' sign alone, or 1 cm or more calf asym- metry alone was 55 to 80%, but the specificity was only 49%. The combination of one of these signs plus 1 cm or more ipsilateral calf asymmetry increased the specificity to 87%, but decreased the sensi- tivity to 15–33%. The specificity increased to 91% with one of these signs in combination with 2 cm or more calf asymmetry. Only 3– 10% of patients had one or more qualitative signs plus 3 cm or more ipsilateral calf asymmetry: in these the specificity for DVT was 96%. Other clinical features of DVT, whose sensitivity and specificity have not been tested, include increased temperature on the affected side, cyanotic discoloration of the limb, and persistent engorgement of superficial veins. Superficial varicose veins almost always empty when the patient lies down: if they remain engorged, this suggests problems with drainage through the deep veins. In very rare cases, tense venous oedema can cause arterial compression and venous gangrene. Differential diagnosis The clinical diagnosis of DVT is not always straightforward. Many of the findings described earlier can also be found in those

16.16.1 Deep venous thrombosis and pulmonary embolism 3713 with muscular strains and bruising, ruptured Baker's cyst, or plantaris tendon, superficial thrombophlebitis, cellulitis, and other traumatic conditions. The presence of bruising near either malleolus suggests ruptured Baker's cyst or other cause of calf haematoma. Given the sinister nature of untreated DVT it is important to con- firm or refute (so far as is possible) the diagnosis with appropriate investigations whenever clinical suspicion is aroused, unless the general condition of the patient makes this inappropriate. Investigation Detection of evidence of thrombus within the circulation: D-dimer D-dimer is a specific degradation product released into the cir- culation by endogenous fibrinolysis of a cross-linked fibrin clot. A D-dimer measured by enzyme-linked immunosorbent assay (ELISA) below a cut-off of 300–540 ng/ml (the values differ slightly from one study to another) make the diagnosis of DVT (or PE) un- likely. However, a concentration of D-dimer above the cut-off level is not useful for making a positive diagnosis because of the large number of false-positive tests. Conventional ELISA assays are cumbersome and not suited for emergency use, which limited the practical utility of D-dimer meas- urements until the development of rapid ELISA assays. These pro- vide the best balance of sensitivity and specificity among the various assays for the safe diagnostic handling of patients with suspected DVT and PE. Detection of the physical presence of thrombus in leg veins The 'gold standard' is contrast venography, but this can be unpleasant for patients, is time consuming for radiology departments, and ex- pensive, hence it is now rarely performed except as part of research protocols. It has been replaced by B-mode ultrasonography as the preferred first-line diagnostic technique. Among patients with DVT proven by contrast venography, B-mode ultrasonography using compression showed a 95% sensitivity in symptomatic patients. In asymptomatic patients who were evaluated because of a high risk of DVT, venous compression ultrasound showed a sensitivity of only Table 16.16.1.1 Pretest clinical probability scoring system and care pathway for the patient with suspected deep venous thrombosis (a) Pretest probability score Criteria Score Active cancer +1 Paralysis, plaster cast +1 Bed rest >3 days, surgery within 4 weeks +1 Tenderness along veins +1 Entire leg swollen +1 Calf swollen >3 cm +1 Pitting oedema +1 Collateral veins +1 Alternative diagnosis likely –2 (b) Pretest probability Low 0 Moderate 1 or 2 High 3 or more (c) Management algorithm Pretest probability score Action Result Further action 0 or 1 Perform D-dimer Negative No further investigation Positive Perform

ultrasonography 2 or more Do not perform D-dimer Perform ultrasonography Negative Withhold treatment and repeat ultrasonography in 10–14 days.
If serial ultrasonography is negative, PE rarely occurs Positive Diagnosis of venous thrombosis established Notes

1. Pretest probability score from Wells et al. (1997).
2. This management algorithm is typical of many used, but further prospective evaluation is warranted.
3. If the physician's judgement is that DVT is very likely in a particular case, then they should proceed to investigations directed at detecting thrombus in leg veins whatever the scoring algorithm would suggest. If the result of ultrasonography is negative, and repeat ultrasonography in 10–14 days is also negative, PE rarely occurs.
4. All patients who are discharged with 'DVT excluded' should be given written information describing how they can be reassessed if symptoms worsen or fail to settle over the next few days. Thromboembolic events have been linked to oestrogen-containing oral contraceptives, but the absolute risk is low and their frequency has been reduced with the use of preparations that contain less than 50 µg of oestrogen. Oral contraceptives may increase the risk of venous thromboembolism after surgery even if their oestrogen content is low.

section 16 Cardiovascular disorders 3714 67%. Regarding veins of the calves, venous compression ultrasound was 93% sensitive in symptomatic patients, but only 26% sensitive in asymptomatic high-risk patients subsequently found to have DVT. In all instances, specificity was 97–99%. Venous-phase contrast-enhanced spiral CT is useful for imaging the veins of the pelvis and thighs, particularly in combination with spiral CT pulmonary angiograms. This offers a comprehensive study for thromboembolism, but increases exposure to ionizing radiation, hence CT pulmonary angiography is not typically accompanied by CT venography. Gadolinium-enhanced magnetic resonance (MR) venography fol- lowing an intravenous injection was sensitive for DVT in the veins of the thighs and pelvis but often technically inadequate. Specificity was 95 to 100%. Usage is restricted by cost, availability, and risk of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in patients with poor renal function. Fibrinogen-uptake radionuclide scanning was used extensively in the 1960s. It is more sensitive for DVT in the calves than in the thighs, meaning that its value is limited because of the greater risk of PE with DVT in the thighs than in the calves. Strategy for diagnosis Management algorithms have been developed to identify patients at low risk of DVT who can be spared extensive testing. These algo- rithms typically use scoring systems to stratify the clinical probability that the particular patient has a DVT and then proceed to D-dimer testing of those with low probability. Patients with a low clinical prob- ability and a negative D-dimer test should not be investigated further for thromboembolic disease. Patients with a high or moderately high clinical probability, or a low clinical probability but elevated D-dimer, proceed to tests for the presence of thrombus in the leg veins, typic- ally by ultrasonography. An example of a pretest scoring system and management algorithm is shown in Table 16.16.1.1. Prevention The prevention of DVT is critical in the prevention of PE. Risk fac- tors for DVT are almost certainly the same as those for PE (see later section in this chapter). Recommendations for the prevention of DVT are shown in Tables 16.16.1.2–16.16.1.7. Despite recommendations for the prevention of DVT in hospitalized patients, an increase in sec- ondary DVT in patients hospitalized in the United States of America from 1991 through 2006 suggests that efforts to prevent DVT in high- risk patients are

inadequate (Fig. 16.16.1.1). In the United Kingdom, recognition of such inadequacy has led commissioners of healthcare to mandate use of a risk scoring tool for venous thromboembolism in all patients admitted to hospital, with the possibility of financial penalties for those that do not achieve a very high rate of compliance. Treatment Proximal DVT leads to PE more frequently than DVT confined to the calf. Patients with acute isolated calf vein DVT without severe symp- toms or risk for extension can be followed with serial noninvasive testing for 2 weeks without treatment with anticoagulants unless there is extension. If such imaging reveals extension to the proximal veins, or extension within the distal veins, then anticoagulation is recommended. Table 16.16.1.2 Recommendations for prevention of venous thromboembolism in patients undergoing general, abdominal–pelvic, cardiac, and thoracic surgery Indication Recommendation General and abdominal–pelvic surgery Very low risk for VTE Early ambulation Low risk for VTE Mechanical prophylaxis, preferably intermittent pneumatic compression Moderate risk for VTE, not high risk for major bleeding LMWH or low-dose unfractionated heparin or mechanical prophylaxis, preferably with intermittent pneumatic compression Moderate risk for VTE, high risk for major bleeding Mechanical prophylaxis, preferably with intermittent pneumatic compression High risk for VTE, not high risk for major bleeding LMWH or low-dose unfractionated heparin and elastic stockings or intermittent pneumatic compression High risk for VTE, cancer surgery, not high risk for major bleeding LMWH, 4 weeks High-risk for VTE, high risk for major bleeding Mechanical prophylaxis, preferably with intermittent pneumatic compression. Start LMWH or low-dose unfractionated heparin when risk of bleeding diminishes Cardiac surgery Uncomplicated Mechanical prophylaxis, preferably with intermittent pneumatic compression Complicated LMWH or low-dose unfractionated heparin and mechanical prophylaxis, preferably with intermittent pneumatic compression Thoracic surgery Moderate risk for VTE, not high risk for bleeding Low-dose unfractionated heparin or LMWH or intermittent pneumatic compression High risk for VTE, not high risk for bleeding LMWH or low-dose unfractionated heparin and intermittent pneumatic compression or elastic stockings High risk for VTE, high risk for bleeding Mechanical prophylaxis, preferably with intermittent pneumatic compression. Start LMWH or low-dose unfractionated heparin when risk of bleeding diminishes LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. Adapted from Guyatt GH, et al. (2012). Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), 7S–47S.

 Table 16.16.1.3 Recommendations for prevention of venous thromboembolism in patients undergoing orthopaedic surgery Surgical procedure Recommendation Total hip arthroplasty or total knee arthroplasty LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin, adjusted-dose vitamin K antagonist, aspirin, or intermittent pneumatic compression for minimum of 10–14 days, preferably up to 35 days. LMWH is the preferred antithrombotic agent. Antithrombotic agent and intermittent pneumatic compression recommended in hospital. Intermittent pneumatic compression only if high risk of bleeding. Suggest against inferior vena cava filter even if contraindication to both pharmacological and mechanical thromboprophylaxis. Hip fracture surgery LMWH, fondaparinux, low-dose unfractionated heparin, adjusted-dose vitamin K antagonist, aspirin, or intermittent pneumatic compression for minimum of 10–14 days and preferably up to 35 days. LMWH is the preferred antithrombotic agent. Knee arthroscopy, no history of prior venous thromboembolism No thromboprophylaxis INR, international normalized ratio; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. Adapted from Guyatt GH, et al. (2012). Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), 7S–47S. Table 16.16.1.4 Recommendations for prevention of venous thromboembolism in patients undergoing neurosurgery Surgical procedure Recommendation Spinal surgery or craniotomy Not high risk for VTE Mechanical prophylaxis, preferably with intermittent pneumatic compression High risk for VTE Mechanical prophylaxis, preferably with intermittent pneumatic compression and pharmacological prophylaxis after risk of bleeding decreases LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. Adapted from Guyatt GH, et al. (2012). Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), 7S–47S. Table 16.16.1.5 Recommendations for prevention of venous thromboembolism in patients following major trauma, traumatic brain injury, acute spinal cord injury Indication Recommendation Major trauma LMWH or low-dose unfractionated heparin or mechanical prophylaxis, preferably with intermittent pneumatic compression.
Inferior vena cava filter should not be used for primary prevention of VTE Major trauma, high risk for VTE LMWH or low-dose unfractionated heparin and mechanical prophylaxis. Mechanical prophylaxis only, preferably with intermittent pneumatic compression, if high risk of bleeding. Add LMWH or unfractionated heparin when risk of bleeding diminishes INR, international normalized ratio; LMWH, low-molecular-weight heparin. VTE, venous thromboembolism Adapted from Guyatt GH, et al. (2012). Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), 7S–47S.
Table 16.16.1.6 Recommendations for prevention of venous thromboembolism in patients with medical conditions Medical conditions in hospital Recommendation Acutely ill hospitalized medical patients, low risk of VTE No prophylaxis Acutely ill hospitalized medical patients, increased risk of VTE Low-dose unfractionated heparin, LMWH, or fondaparinux. Compression stockings or intermittent pneumatic compression if high risk of bleeding Critically ill, critical care unit Low-dose unfractionated heparin or LMWH Critically ill, critical care unit, high-risk bleeding Compression stockings and/or intermittent pneumatic compression. Pharmacological prophylaxis when risk of bleeding decreases Chronically immobilized, nursing home, or at home No thromboprophylaxis Outpatients, solid tumours, and additional risk factors for VTE LMWH or low-dose unfractionated heparin Outpatients, thrombophilia, no prior VTE No thromboprophylaxis LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. Adapted from Guyatt GH, et al. (2012). Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), 7S–47S.

section 16 Cardiovascular disorders 3716 Recommendations for treatment are shown in Table 16.16.1.8, with further details discussed in Chapter 16.16.2. With generally increasing pressure to avoid hospital admission, or to keep admis- sions as short as possible, some patients with a primary diagnosis of PE or DVT who are being treated with vitamin K antagonists, dabigatran or edoxaban are being discharged from hospital before adequate heparin can be administered, and before vitamin K antag- onists can become antithrombotic. An increased mortality has been observed among patients with PE discharged in 4 days or fewer if inadequately treated, hence if patients are to be discharged before adequate heparin can be admin- istered, outpatient treatment with low-molecular-weight heparin (LMWH) for at least 5 days should be administered if dabigatran or edoxaban are to be used and until the international normalized ratio (INR) is ≥2.0 for 24 hours if a vitamin K antagonist is em- ployed. Extended outpatient treatment with LMWH may be con- sidered as well as treatment with novel oral anticoagulants. Clinical trials of dabigatran and edoxaban required a lead in with paren- teral anticoagulants for at least 5 days, hence there is no

evidence to support the immediate use of these drugs without prior paren- teral anticoagulation. By contrast, rivaroxaban and apixaban do not require prior treatment with parenteral anticoagulants, although in clinical trials these had been given to most patients for 1 or 2 days before randomization. Complications DVT itself carries extensive morbidity irrespective of PE. Severe post-phlebitic syndrome (venous ulcer or combinations of pain, cramps, heaviness, pruritus, paraesthesia, pretibial oedema, in- duration, hyperpigmentation, venous ectasia, redness, or pain with calf compression) occurs in 9% of patients by 5 years after a 3-month course of treatment with anticoagulants. A multicentre placebo-controlled trial found that routine use of graduated compression stockings did not reduce the incidence of post- thrombotic syndrome, hence these are no longer recommended. Compression stockings might, however, have reduced symptoms of acute DVT or symptoms of post-thrombotic syndrome in those who developed it. Acute pulmonary embolism Incidence Acute PE is the third most common cardiovascular problem after coronary heart disease and stroke. In 2008, 0.9% of patients aged 18 years or more hospitalized in short-stay hospitals in the United States of America had PE. This represented 135 patients per 100 000 adult population. Age-adjusted rates were similar in men and women. Silent PE, on average, was diagnosed in 36% of patients with proximal DVT and 13% with distal DVT. The incidence of acute PE increases exponentially with age and is much more frequent in adults than in children, but it is not rare in children. In autopsy studies encompassing university as well as non- university hospitals, when the pathologist judged that PE con- tributed to death or caused death, the diagnosis was unsuspected ante-mortem in over one-half of cases. Some of these were in patients who died of malignancy, in whom a diagnosis of PE may (appropri- ately) not have been actively pursued. However, the time-honoured point remains as valid today as ever: a high index of suspicion is necessary to reduce the number of patients with unsuspected PE. Predisposing factors Immobilization, irrespective of the cause, is the most frequent predisposing factor (Table 16.16.1.9). Immobilization of even 1 or 2 days may predispose to PE and most patients with PE are immo- bilized less than 2 weeks. Obesity is also a risk factor. Pregnancy-associated DVT has increased in recent years, the rate being over twice that in nonpregnant women. The rate of DVT following caesarean section is twice the rate following vaginal de- livery. By contrast, higher rates of PE have not been shown in preg- nancy, but this may be because of reluctance to perform imaging studies in pregnant women. There has been much interest in the subject of genetic pre disposition to thromboembolism. Heterozygosity for the factor V Leiden mutation increases susceptibility three-to eight- fold in a variety of circumstances. Other genetic and acquired thrombophilic factors include protein C deficiency, protein S deficiency, antithrombin deficiency, prothrombin 20 201A, high concentration of factor VIII, hyperhomocystinaemia, hep- arin cofactor II deficiency, dysfibrinogenaemia, decreased levels of plasminogen, decreased levels of plasminogen activators, antiphospholipid antibodies, heparin-induced thrombocyto- penia, and myeloproliferative disorders. For full discussion of these and related issues, see Chapter 22.7.4. Table 16.16.1.7 Recommendations for prevention of venous thromboembolism during long-distance air travel Long-distance travel Frequent ambulation, calf muscle exercise Additional risk factors for VTE Frequent ambulation, calf muscle exercise, and below-knee graduated compression stockings providing 15–30 mm Hg of pressure at ankle. Recommend against aspirin or anticoagulants LMWH, low-molecular-weight heparin; VTE, venous thromboembolism. Adapted from Guyatt GH, et al. (2012). Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), 7S–47S. 175 25 1986 1996 2006 75 125 DVT/100 000 population Principal Dx DVT Secondary Dx DVT All DVT Dx Fig. 16.16.1.1 Population-based prevalence of deep venous

thrombosis (DVT) in the United States of America according to year. Incidence of principal diagnosis of DVT (admitting diagnosis) did not change from 1986 to 2006. Secondary diagnoses of DVT (occurring during hospitalization) increased. Total incidence of DVT increased in parallel. Grey bars, principal diagnosis DVT; white bars, secondary diagnosis DVT; black bars, all DVT diagnoses. Data from Stein PD, Matta F, Dalen JE (2011). Is the campaign to prevent venous thromboembolism in hospitalized patients working? Chest, 139, 1317–21.

16.16.1 Deep venous thrombosis and pulmonary embolism 3717 Clinical features The clinical characteristics of acute PE have been derived from pro- spectively acquired data of patients recruited in trials of diagnostic investigations or therapies such as the PIOPED studies. Such trials clearly only include those in whom there was sufficient clinical sus- picion to lead physicians to obtain diagnostic tests: whether subtle PE was overlooked is undetermined. The specificity of signs, symp- toms, and ordinary clinical tests was low among patients with sus- pected PE in whom the diagnosis was eventually excluded. Symptoms In patients in whom the diagnosis is not confused by pre-existing cardiac or pulmonary disease, dyspnoea is the most common symptom, occurring in 73% of cases both in PIOPED and PIOPED II (Table 16.16.1.10), with dyspnoea only on exertion in 16%. Dyspnoea (at rest or during exertion) and orthopnoea were more frequent in patients with PE in main or lobar pulmonary arteries than in patients in whom the largest vessel with PE was a segmental pulmonary artery. The onset of dyspnoea occurred within seconds Table 16.16.1.8 Recommendations for treatment of venous thromboembolism and/or pulmonary thromboembolism Condition Treatment High clinical suspicion of DVT or PE or intermediate clinical suspicion if results of diagnostic tests delayed >4 h Give anticoagulants while awaiting outcome of diagnostic tests. Confirmed proximal DVT or PE and no cancer Suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist. Initial treatment with parenteral anticoagulation is required for dabigatran, and edoxaban. Confirmed proximal DVT or PE and cancer Suggest LMWH over vitamin K antagonist, dabigatran, rivaroxaban, apixaban, or edoxaban. Suggest LMWH once daily rather than twice daily. Start vitamin K antagonists with LMWH, unfractionated heparin or fondaparinux on first treatment day. Treat PE or DVT with anticoagulants for 3 months if provoked by surgery or a transient risk factor. Treat a first unprovoked PE or DVT for longer than 3 months if a low or moderate risk of bleeding, and for 3 months if a high-risk of bleeding. Treat DVT or PE associated with active cancer for longer than 3 months. In patients with an unprovoked DVT or PE who are stopping anticoagulant therapy, aspirin may help prevent recurrent PE or DVT, but it is less effective than anticoagulants. Compression stockings are not recommended for routine use to prevent post-thrombotic syndrome. Recommend against inferior vena cava filter in patients with DVT unless contraindication to anticoagulants. Acute proximal DVT Suggest anticoagulants alone over catheter directed or systemic thrombolysis or operative thrombectomy. Acute proximal DVT Home treatment if circumstances adequate. Recurrent PE or DVT The generally accepted consensus recommendation is to insert an inferior vena cava filter if patient has recurrent PE. Some, to avoid a filter, suggest LMWH if recurrent PE or DVT occurs while on a non-LMWH anticoagulant. If recurrent PE or DVT occurs while on LMWH, increase the dose of LMWH. Isolated distal DVT Serial imaging for 2 weeks rather than anticoagulation unless severe symptoms or risk factors for proximal extension. Treat with anticoagulants if proximal extension or extension but remaining confined to the distal veins. Distal superficial vein thrombosis, >5 cm Prophylactic doses of fondaparinux of LMWH for 45 days. DVT and low-risk PE In patients with DVT, or low-risk PE, home treatment is recommended if home circumstances are adequate. Massive PE, hypotension (systolic blood pressure <90 mm Hg) or high risk of developing hypotension, no high bleeding risk Systemic thrombolytic therapy,

short infusion time preferred (2 h). Infuse through peripheral vein rather than pulmonary artery. Massive PE, highly compromised patients unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy Catheter extraction or fragmentation or pulmonary embolectomy. Pulmonary embolectomy if failed catheter-assisted embolectomy. Inferior vena cava filter and PE Inferior vena cava filters are recommended for patients with PE if anticoagulants are contraindicated. In most patients with PE, vena cava filters are not recommended. However, the American College of Chest Physicians 2016 guidelines indicated that recommendations against the use of IVC filters in anticoagulated patients with hypotension from severe PE may not apply to this select subgroup. Other subgroups not assessed by randomized controlled are discussed in the section on inferior vena cava filters. LMWH, low-molecular-weight heparin. Modified from Kearon C, et al. (2012). Antithrombotic therapy for VTE disease. Antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(suppl), e419S–e494S and from Kearon C, et al. (2016). Antithrombotic therapy for VTE disease: Chest guideline and expert panel report. Chest, 149, 315–52.

section 16 Cardiovascular disorders 3718 or minutes in 72% of cases, and within seconds, minutes, or hours in 83%. In some, however, the onset of dyspnoea occurred over days. Pleuritic chest pain (66% of patients with PE and no pre-existing cardiopulmonary disease in PIOPED and 44% in PIOPED II) oc- curred much more often than haemoptysis (13% in PIOPED and 5% in PIOPED II). Cough was common (37% and 34% in PIOPED and PIOPED II) among patients with PE and no pre-existing cardiopulmonary disease. This was nonproductive or productive of bloody (typically blood-streaked, but it can be pure blood or blood-tinged) or puru- lent (5% of cases) sputum. Signs Tachypnoea (respiratory rate ≥20/min) was the most common sign of acute PE among patients with no prior cardiac or pul- monary disease (70% of patients in PIOPED and 54% in PIOPED II) (Table 16.16.1.11). Tachycardia (heart rate >100/min) occurred in 30% and 24% of patients with PE in PIOPED and PIOPED II, and the pulmonary component of the second sound was accentuated in 23% and 15% of cases. DVT was clinically apparent in 11% of pa- tients with PE in PIOPED, but more frequently in PIOPED II (47%). A right ventricular lift, third heart sound, or pleural friction rub were uncommon, each occurring in 4% or less of patients with PE. Most patients with PE who had rales (crepitations) had pul- monary parenchymal abnormalities, atelectasis, or a pleural effusion on the chest radiograph. Among patients with PE and no other source of fever, temperature 39.9°C or lower was present in 99.7% and fever of 40.0°C or higher occurred in 0.3%. Temperature 37.7°C or less was present in 86%. Fever in patients with pulmonary haemorrhage/infarction was not more frequent than among those with no pulmonary haemorrhage/ infarction. Clinical evidence of DVT was often present in patients with PE and otherwise unexplained fever. Circulatory collapse (systolic blood pressure <80 mm Hg or loss of consciousness) was an uncommon mode of presentation: 15% in PIOPED and in 8% in PIOPED II. However, patients with circula- tory collapse may not be candidates for recruitment into trials of diagnostic investigations or therapies, and patients with circulatory collapse often die within the first few hours, hence it may be that the incidence of circulatory collapse as determined from published series is falsely low. Patients with pulmonary infarction have less se- vere PE than patients with isolated dyspnoea, and those with circu- latory collapse probably have the most severe of all. Combinations of symptoms and signs Dyspnoea or tachypnoea (respiratory rate ≥20/min) was present in 90% and 84% of patients with acute PE and no pre-existing cardiac or pulmonary disease in PIOPED and PIOPED II. Dyspnoea or tach- ypnoea or pleuritic pain was present in 97% and 92%, respectively. Dyspnoea or tachypnoea

or pleuritic pain or radiographic evidence Table 16.16.1.9 Predisposing factors for pulmonary embolism in all patients irrespective of previous cardiac or pulmonary disease (n = 383) Predisposing factor Cases (%) Immobilization 54 Surgery 42 Lung disease 27 Malignancy 18 Coronary heart disease 20 Thrombophlebitis—ever 19 Myocardial infarction 13 Trauma—lower extremities 12 Heart failure 12 Chronic obstructive pulmonary disease 10 Stroke 10 Asthma 7 Pneumonia—acute 7 Prior PE 6 Oestrogen 6 Collagen vascular disease 4 Postpartum—3 months or less 2 Interstitial lung disease 2 Unpublished data from PIOPED in Stein PD (2016). Pulmonary embolism, 3rd edn. Wiley Blackwell, Oxford. Table 16.16.1.10 Symptoms of pulmonary embolism in patients without pre-existing cardiac or pulmonary disease Symptoms PE (%) PIOPED I (n = 117) PIOPED II
(n = 127–133) Dyspnoea Dyspnoea (rest or exertion) 73 73 Dyspnoea (at rest) 55 Dyspnoea (exertion only) 16 Orthopnoea (≥2 pillow) 28 Pleuritic pain 66 44 Chest pain (not pleuritic) 4 19 Cough 37 34 Haemoptysis 13 5a Purulent 5 Clear 5 Nonproductive 20 Wheezing 9 21 Palpitations 10 Calf or thigh swelling 41 Calf swelling only 28 33 Calf and thigh swelling 7 Thigh swelling only 1 Calf or thigh pain 44 Calf pain only 26b 23 Calf and thigh pain 17 Thigh pain only 3 a Haemoptysis, patients with PE: 2, slightly pinkish; 4, blood-streaked; 1, all blood
(<1 teaspoonful). b ‘Leg pain’. Data from Stein PD, et al. (1991). Clinical, laboratory, roentgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no
pre-existing cardiac or pulmonary disease. Chest, 100, 598–603 and Stein PD, et al. (2007). Clinical characteristics of patient with acute pulmonary embolism: data from PIOPED II. Am J Med, 120, 871–9.

16.16.1 Deep venous thrombosis and pulmonary embolism 3719 of atelectasis or a parenchymal abnormality was present in 98%. The remaining patients usually had either DVT or an unexplained low Pao2. PE was rarely diagnosed in the absence of dyspnoea or tachyp- noea or pleuritic pain. Dyspnoea or tachypnoea occurred in 92% of all patients with PE (irrespective of pre-existing cardiopulmonary disease) in whom the pulmonary emboli were in main or lobar pulmonary arteries, but in only 65% of patients in whom the largest PE was in segmental pul- monary arteries. Dyspnoea or tachypnoea or pleuritic pain occurred in 97% of patients with proximal PE and 77% of patients with pul- monary emboli in only segmental pulmonary arteries. Accuracy of clinical assessment To emphasize the point that the diagnosis of PE is difficult to make, senior staff physicians and postgraduate fellows taking part in the PIOPED study were uncertain of the diagnosis in most patients. Using individual judgement without any specific predetermined criteria, senior staff were correct in the diagnosis in 88% of cases when their clinical assessment indicated a high probability of PE. When their clinical assessment indicated a low probability of PE, senior staff correctly excluded PE in 86%. Postgraduate fellows, on the basis of clinical assessment, were more accurate in excluding PE than they were in making the diagnosis. Objective scoring systems for the probability of acute PE give probability assessments similar to those of experienced physicians and do not require experience or clinical judgement. An example of a scoring system that is mostly objective is shown in Table 16.16.1.12. Differential diagnosis The commonest presentation of acute PE is with dyspnoea and/or pleuritic chest pain. There are several other possible causes of these symptoms, the commonest being musculoskeletal pain and pneu- monia. Musculoskeletal chest pain can be very similar to that caused by pleurisy, and splinting of the chest can lead to a perception of breathlessness that may be exacerbated by anxiety. If there is an obvious history of local trauma to the chest, then the patient will rarely present to the physician,

but it is worthwhile to ask specifically whether there has been any trauma or unaccustomed physical ac- tivity, whether the pain can be brought on by particular movements, and to examine carefully for local tenderness of the ribs, muscles, or costal margins. However, tenderness can sometimes be found in cases of pleurisy, and chest pain was reproduced by palpation in 20% of patients with PE. Appropriate history often supports a diagnosis of musculoskeletal pain. Pneumonia complicated by pleurisy can cause dyspnoea and chest pain. Important features to look for in the history include pre- ceding systemic upset (flu-like symptoms), high fever, and rigors, and on examination, high fever, 'toxic appearance', and chest signs of pneumonic consolidation. If a positive diagnosis of another cause of dyspnoea and/or pleuritic chest pain cannot be made, then the default position should be to assume that the patient has PE until proven otherwise.

Table 16.16.1.11 Signs of pulmonary embolism in patients without pre-existing cardiac or pulmonary disease

Signs	PE (%)	PIOPED I (n = 117)	PIOPED II (n = 127–133)
General			
Tachypnoea (≥20/min)	70	54	
Tachycardia (>100/min)	30	24	
Diaphoresis	11	2	
Cyanosis	1	0	
Temperature >38.5°C (>101.3°F)	7	1	
Cardiac examination (any abnormality)	21		
Increased P2	23	15	
Third heart sound	3		
Fourth heart sound	24		
Right ventricular lift	4	4	
Jugular venous distension	14		
Lung examination (any abnormality)	29		
Rales (crackles)	51	18	
Wheezes	5	2	
Rhonchi	2		
Decreased breath sounds	17		
Pleural friction rub	3	0	
DVT			
Calf or thigh	11	47a	
Calf only	32		
Calf and thigh	14		
Thigh only	2		
Homans' sign	4		

P2, pulmonary component of second sound. a Number of patients with PE who had one or more signs of DVT: oedema, 55; erythema, 5; tenderness, 32; palpable cord, 2. Data from Stein PD, et al. (1991). Clinical, laboratory, roentgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest, 100, 598–603 and Stein PD, et al. (2007). Clinical characteristics of patient with acute pulmonary embolism: data from PIOPED II. Am J Med, 120, 871–9.

Table 16.16.1.12 A model to determine the clinical probability of pulmonary embolism according to Wells and associates

Clinical feature	Score (points)
Clinical signs and symptoms of DVT (objectively measured leg swelling and pain with palpation in the deep vein system)	3.0
Heart rate>100/min	1.5
Immobilization ≥3 consecutive days (bed rest except to access bathroom) or surgery in previous 4 weeks	1.5
Previous objectively diagnosed PE or DVT	1.5
Haemoptysis	1.0
Malignancy (cancer patients receiving treatment within 6 months or receiving palliative treatment)	1.0
PE as likely or more likely than alternative diagnosis (based on history, physical examination, chest radiograph, ECG, and blood tests)	3.0

Score: <2.0, low probability; ≤4, unlikely probability; >4, likely probability; >6.0, high probability. Data from Wells PS, et al. (2000). Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost, 83, 416–20 and from Wells PS, et al. (2001). Excluding PE at the bedside without diagnostic imaging: management of patients with suspected PE presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med, 135, 98–107.

Investigation

Detection of evidence of thrombus within the circulation: D-dimer

As when considering the diagnosis of DVT, a 'negative' D-dimer test is useful for excluding PE in patients who are clinically thought to be at low risk, but a 'positive' result does not establish the diagnosis. Hence, when used in the appropriate clinical context, D-dimer testing is useful in defining a group of patients with suspected PE who do not require further investigation. In ranking the D-dimer assays according to their sensitivity values and likelihood of increasing certainty for ruling out PE, the ELISA and quantitative rapid ELISA assays are significantly su- perior to the semiquantitative latex and whole-blood agglutination assays. The

quantitative rapid ELISA assay is more convenient than the conventional ELISA and provides a high level of certainty for a negative diagnosis of PE as well as DVT. A particle-enhanced immunoturbidometric assay (quantitative latex agglutination) gives results comparable to the rapid ELISA. The 3-month risk of PE in untreated patients with a negative rapid ELISA D-dimer measurement and low or intermediate clin- ical probability Geneva score was 0% (0 of 220). With a negative D-dimer by rapid ELISA or quantitative latex agglutination assay and an unlikely (≤4) Wells score, PE occurred in 0.4% (4 of 1028), and with an unlikely (≤10) revised Geneva score in 1 of 320 (0.3%). Detection of the physical presence of thrombus in the pulmonary circulation Ventilation–perfusion lung scans By 2001 in the United States of America the use of CT pulmonary angi- ography surpassed the use of ventilation–perfusion lung scans for the diagnosis of acute PE, the use of ventilation–perfusion lung scans having fallen into disfavour after the PIOPED trial because in most patients they led to an indeterminate result. Now, two decades since PIOPED was published, advances have been made in imaging equipment, improved methods of interpretation, and new radiopharmaceuticals. With such advances, and recognizing the risk of radiation with CT angiography, radionuclear imaging is receiving renewed interest. Based on the results of PIOPED, a high-probability lung ventilation–perfusion scan (Fig. 16.16.1.2) indicates PE in 87% of patients (Table 16.16.1.13) and a normal scan excludes PE. In the absence of any other information an intermediate probability scan indicates a 30% chance of PE and a low-probability scan of 14%. A low-probability ventilation–perfusion scan by the criteria used in PIOPED does not therefore exclude PE. Intermediate and low-probability interpretations may be grouped as ‘nondiagnostic’, which was frequently the case in PIOPED. Prior clinical assessment in combination with interpretation of the ventilation–perfusion scan improves diagnostic validity (Table 16.16.1.13). If the ventilation–perfusion scan is interpreted as high probability for PE, and if the clinical impression is concord- antly high, then the positive predictive value for PE is 96%. If the ventilation–perfusion scan is low probability and the clinical sus- picion is concordantly low, then PE is excluded in 96% of patients. The probability of PE can be determined based on the number of mismatched defects. Since PIOPED, criteria for the interpretation of very low probability lung scans (positive predictive value <10%) have been developed and tested. Fewer mismatched perfusion defects are required to diagnose PE among patients with no prior cardiopul- monary disease. Adding clinical assessment to the stratification re- sults in a more accurate evaluation. Outcome studies, as opposed to studies of accuracy as was PIOPED, showed that in patients with low probability, very low probability, or normal ventilation–perfusion lung scans there was no fatal PE and nonfatal PE in only 0.17% after 3–12 months without anticoagulants. Using revised PIOPED criteria, some have shown that in patients with suspected acute PE and a normal chest radiograph the perfu- sion lung scan was diagnostic (high probability, normal, or very low probability) in 89% of patients (Table 16.16.1.14). There were no nondiagnostic perfusion scans when interpreted by the PISAPED criteria (Table 16.16.1.15). After elimination of nondiagnostic scans, sensitivity with modified PIOPED criteria was 86% and specificity was 93%. With PISAPED criteria, sensitivity was 72% and specificity was 97%. It may be, therefore, that with updated techniques, perfu- sion scintigraphy in a patient with a normal chest radiograph can provide diagnostic accuracy similar to CT angiography at a lower cost and with a lower radiation dose. Although not routine practice in most centres, it can be useful to obtain a post-therapy baseline ventilation–perfusion lung scan for use in the event of suspected recurrent PE. This will Fig. 16.16.1.2 Ventilation lung scan (left panel) and perfusion lung scan (right panel): posterior views with left (L) and right (R) indicated. The ventilation scan, equilibrium phase, shows nearly normal ventilation. The perfusion scan shows absent perfusion in the left lower lobe and mismatched perfusion defects in the left upper lobe.

Perfusion defects (grey areas) are also shown in the right lung. This ventilation–perfusion lung scan was interpreted as showing high probability for PE.

16.16.1 Deep venous thrombosis and pulmonary embolism 3721 assist in determining if abnormalities subsequently discovered on a ventilation–perfusion scan are new or residual. A residual abnor- mality of perfusion 1 year after PE is more frequent among patients with prior cardiopulmonary disease than among patients with none. SPECT ventilation–perfusion lung scan imaging Single-photon emission computed tomography (SPECT) ventilation–perfusion lung scan imaging may further improve the accuracy of pulmonary scintigraphy. SPECT offers the advantages of tomographic sections over traditional planar ventilation– perfusion imaging. The ability to obtain SPECT lung scans was still in its relatively early stages when the PIOPED investigation of planar lung scans was published. Dual- and triple-headed gamma cameras with ultrahigh-resolution collimators have been devel- oped, as have new radiopharmaceuticals for ventilatory studies, prominent among which is 99mTc-Technegas (Cyclomedica, Lucas Heights, Australia), which consists of ultrafine carbon particles that behave physiologically like a gas. Many investigators have found SPECT ventilation–perfusion lung scan imaging to be better than planar imaging. Among its ad- vantages are the avoidance of overlapping of small perfusion de- fects by normal tissue and a higher contrast resolution than planar scans. It can, therefore, detect abnormalities—particularly at the subsegmental level and in the lung bases—where the segments are tightly packed. Review showed that the sensitivity of SPECT was higher than planar lung scans in 4 of 5 investigations, and specifi- city was generally higher, equal, or only somewhat lower than planar ventilation–perfusion lung scans. Nondiagnostic SPECT lung scans were reported in ≤3% by most investigators. Pulmonary angiography Pulmonary angiography is no longer the diagnostic gold standard for PE (Fig. 16.16.1.3). It is associated with serious complications in about 1% of patients and has been replaced by contrast-enhanced CT. Contrast-enhanced spiral CT The sensitivity of multidetector (mostly 4-detector) CT angiography alone and in combination with CT venous-phase venography was in- vestigated in PIOPED II. The CT angiogram among 824 patients was of insufficient quality for a conclusive interpretation in 6.2%. Among 773 patients with an adequate CT angiogram, the sensitivity of CT angiography was 83% and specificity was 96% (Fig. 16.16.1.4): posi- tive predictive value was 86% and negative predictive value was 95%. Positive predictive values were 97% for PE in a main or lobar artery, 68% in those in whom the largest vessel with PE was a segmental pulmonary artery, and 25% among only a few patients in whom the largest PE was in a subsegmental branch. Table 16.16.1.13 The probability of pulmonary embolism using clinical assessment in combination with ventilation–perfusion lung scans Clinical science probability (%) 80–100 20–79 0–19 All probabilities Scan category PE+/No of patientsa % PE+/No of patients % PE+/No of patients % PE+/No of patients % High probability 28/29 96 70/80 88 5/9 56 103/118 87 Intermediate probability 27/41 66 66/236 28 11/68 16 104/345 30 Low probability 6/15 40 30/191 16 4/90 4 40/296 14 Near normal/normal 0/5 0 4/62 6 1/61 2 5/128 4 Total 61/90 68 170/569 30 21/228 9 252/887 28 a PE+ indicates angiogram reading that shows PE or determination of PE by the outcome classification committee on review. PE status is based on angiogram interpretation for 713 patients, on angiogram interpretation and outcome classification committee reassignment for 4 patients, and on clinical information alone (without definitive angiography) for 170 patients. Source data from A National Investigation by the PIOPED Investigators (1990). Value of the ventilation/perfusion scan in acute pulmonary embolism—results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). American Medical Association. Table 16.16.1.14 Modified PIOPED II scintigraphic criteria Diagnosis Criteria PE present High probability (≥2 segmental

equivalents of perfusion scan-chest radiograph mismatcha) PE absent Normal perfusion Very low probability Nonsegmental lesion, e.g. prominent hilum, cardiomegaly, elevated diaphragm, linear atelectasis, costophrenic angle effusion with no other perfusion defect in either lung Perfusion defect smaller than radiographic lesion 1–3 small segmental defects A solitary chest radiographic–perfusion scan matched defect in the mid or upper lung zone confined to a single segment Stripe sign around perfusion defect (best tangential view) Pleural effusion ≥ 1/3 of the pleural cavity with no other perfusion defect in either lung Not diagnostic All other findings a May be ≥2 large segmental mismatches, or 1 large and 2 moderate mismatches or 4 moderate segmental mismatches. This research was originally published in JNM. Sostman H et al. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. J Nucl Med. 2008;49(11):1741–8. Table 1. © by the Society of Nuclear Medicine and Molecular Imaging, Inc. Table 16.16.1.15 PISAPED scintigraphic criteria Diagnosis Criteria PE present One or more wedge-shaped perfusion defects PE absent Normal or near normal perfusion Contour defect caused by enlarged heart, mediastinum, or diaphragm Perfusion defect, not wedge-shaped Not diagnostic Cannot classify as PE-positive or PE-negative Modified from Sostman HD, et al. (2008). Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. J Nucl Med, 49, 1741–8.

section 16 Cardiovascular disorders 3722 The combination CT angiogram with venous-phase imaging of the pelvic and thigh veins (CT venogram) among 824 patients was of insufficient quality for a conclusive interpretation in 11%. Among the 737 patients with an adequate CT angiogram/CT venogram combination, the sensitivity was 90% and specificity was 95%, with positive predictive value 85% and negative predictive value 97%. Among patients with suspected PE who were evaluated by 64- detector CT, 10.8% were shown to have PE by CT angiography and an additional 1.3% had venous thromboembolism based on a positive CT venogram with a negative CT angiogram. A 1.3% yield would seem poorly cost effective, but among the patients shown to have venous thromboembolism, 11% were diagnosed only by CT venography, which is a proportion that some would consider sufficiently high to merit consideration of its use. Most, however, believe that CT venography is unnecessary with CT pulmonary angiography, because the risk from radiation outweighs the bene- fits of additional diagnoses. In patients with a high risk of lower- extremity DVT, or elderly patients with low risk of radiation effects and limited cardiopulmonary reserve, CT venography is recom- mended by some. As with ventilation–perfusion scans, better prediction can be made if imaging results are interpreted in the light of clinical information (Table 16.16.1.16). Among patients with a high or intermediate probability prior clinical assessment based on the Wells score, a posi- tive CT angiogram had a positive predictive value for PE of 96% and 92% respectively. In patients with a low or intermediate probability prior clinical assessment and a negative CT angiogram, the negative predictive values for exclusion of PE were 96% and 89% respectively. Positive and negative predictive values were considerably reduced when scan results were discordant with clinical probabilities. MRI Potential advantages of gadolinium-enhanced MR angiography are that it does not involve the use of iodinated contrast agents, it is min- imally invasive, and patients are not exposed to ionizing radiation. In small studies it shows a sensitivity for PE in proximal or segmental branches that ranges from 77% to 100% and specificity that ranges from 95% to 98%, but sensitivity for subsegmental branches was not evaluated prior to PIOPED III. Gadolinium-enhanced venous- phase imaging of the veins of the pelvis and thighs in combination with imaging of the pulmonary arteries would permit a comprehen- sive study for thromboembolism comparable to the combination of contrast-enhanced spiral CT of the pulmonary

arteries in combin- ation with venous-phase CT of the veins of the lower extremities. The PIOPED III trial of the accuracy of gadolinium-enhanced MR pulmonary angiography showed that most centres had diffi- culty in obtaining adequate quality MR pulmonary angiograms (MRA). The investigators defined an adequate quality MRA as ad- equate opacification through subsegmental vessels. Among 371 patients, adequate quality images were obtained in the main or lobar pulmonary arteries in 91%, of the segmental pulmonary ar- teries in 87%, and of the subsegmental branches in 73%. Averaged across participating centres, MRAs were technically inadequate in 25%, but the figure at one centre was only 11%. Including patients with technically inadequate images, MRA identified 57% with PE. Technically adequate MRA had a sensitivity of 78% and specificity of 99%, and the sensitivity of MRA for detecting PE in a main or lobar pulmonary artery was 79%. Pulmonary embolism was rarely identi- fied by MRA when the largest PE was in a segmental or subsegmental branch. Specificity was 98% to 100%, irrespective of the order of the vessel. The combination of a technically adequate MRA with MR venography (MRA/MRV) had a higher sensitivity than MRA alone, Fig. 16.16.1.3 Selective digital subtraction pulmonary angiogram of the left pulmonary artery showing multiple intraluminal filling defects indicative of pulmonary thromboemboli. One of these has been identified with an arrow. Fig. 16.16.1.4 Contrast-enhanced spiral CT showing a large intraluminal filling defect (arrow).

 92%, while maintaining a high specificity of 96%. However, either MRA or MRV was technically inadequate in 52% of patients. This led the investigators to conclude that MRA should only be con- sidered at centres that routinely perform it well, and for patients who have contraindications to standard tests. Nephrogenic systemic fibrosis (also known as nephrogenic fibrosing dermopathy) has been reported in patients with moderate or severe renal failure and in pa- tients on dialysis following MRA with gadolinium-containing con- trast agents. Other diagnostic approaches are recommended in such patients. Other tests Electrocardiography Electrocardiographic (ECG) abnormalities are common in acute PE (Table 16.16.1.17), with a normal ECG found in only 30% of patients. Acute ventricular dilatation is speculated to be the most likely cause of the ECG changes. Abnormalities of the ST segment and T wave are by far the most frequent observation, with nonspecific ST seg- ment or T-wave changes seen in about 50% of patients in whom the severity of PE ranged from mild to severe. Atrial flutter or atrial fib- rillation in patients with acute PE is nearly always limited to individ- uals with prior heart disease. Electrocardiographic manifestations of acute cor pulmonale (S1Q3T3, complete right bundle branch block, P pulmonale, or right axis deviation) are less common than ST-segment or T-wave changes and are not sensitive for right ventricular dilata- tion. One or more of these abnormalities occurred in 26% of patients with submassive or massive acute PE not associated with cardiac or pulmonary disease (32% of patients with massive PE). Left axis devi- ation occurs more frequently than right axis deviation. The ECG may simulate an inferior infarction with Q waves and T-wave inversion in leads II, III, and aVF, or anteroseptal infarction characterized by QS or QR waves in V1 and T-wave inversion in the right precordial leads. The development of Q waves and extensive T-wave inversion in the anterior and lateral leads has also been observed. However, a pseudoinfarction pattern is seen in only 3% of patients. Inversion of the T waves is the most persistent ECG abnormality, disappearing in only 22% of patients 5 or 6 days after the PE was diag-nosed, although resolving in 49% by 2 weeks. Depression of the ST segment tends to resolve somewhat faster, and abnormalities of depolar- ization resolve more quickly than abnormalities of repolarization. Well over half of the ECGs that showed pseudoinfarction, S1S2S3, S1Q3T3, right ventricular hypertrophy, or right bundle branch block no longer show these abnormalities 5 or

6 days after the diagnosis is made. Patients with ST-segment abnormalities, T-wave inversion, pseudoinfarction patterns, S1Q3T3 patterns, incomplete right bundle branch block, right axis deviation, right ventricular hyper- trophy, or ventricular premature beats have larger perfusion defects on the lung scan or larger defects on the pulmonary arteriogram than those with normal ECGs. Such patients have higher pul- monary arterial pressures and in general have a low partial pressure of oxygen in arterial blood. The electrocardiographic abnormalities in patients with PE are not specific, although they may suggest the presence of PE. For ex- ample, patients with pneumonia often show QRS abnormalities or nonspecific ST-segment or T-wave changes comparable to those seen in PE. Chest radiography The findings on the plain chest radiograph—when used together with the history, physical examination, electrocardiogram, and simple Table 16.16.1.16 Positive and negative predictive values of CT pulmonary angiography in relation to prior clinical assessment High clinical probability (Wells score >6) n/N (%) Intermediate clinical probability (Wells score 2–6) n/N (%) Low clinical probabilitya (Wells score <2) n/N (%) CTA positive (positive predictive value) 22/23 (96) 93/101 (92) 22/38 (58) CTA or CTV positive (positive predictive value) 27/28 (96) 100/111 (90) 24/42 (57) CTA negative (negative predictive value) 9/15 (60) 121/136 (89) 158/164 (96)a CTA and CTV negative (negative predictive value) 9/11 (82) 114/124 (92) 146/151 (97)a CTA, CT pulmonary angiography; CTV, CT venous-phase imaging. a To avoid bias for calculation of the negative predictive value in patients with a low-probability prior clinical assessment, only patients with a reference test diagnosis by V/Q scan or conventional pulmonary digital subtraction angiography were included. Modified from Stein PD, et al. (2006). PK for the PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med, 354, 2317–27. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission. Table 16.16.1.17 Electrocardiographic manifestations of pulmonary embolisms in patients without prior cardiac or pulmonary disease (n = 89) Patients with electrocardiographic findingsa (%) Rhythm disturbances Atrial flutter 1 Atrial fibrillation 4 Atrial premature contractions 4 Ventricular premature contractions 4 P wave P pulmonale 2 QRS abnormalities Right axis deviation 2 Left axis deviation 13 Incomplete right bundle branch block 4 Complete right bundle branch block 6 Right ventricular hypertrophy 2 Pseudoinfarction 3 Low voltage (frontal plane) 3 ST segment and T wave Nonspecific ST-segment or T-wave abnormalities 49 a Some patients had more than one abnormality. Data from Stein PD, et al. (1991). Clinical, laboratory, roentgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest, 100, 598–603.

 laboratory tests—assist in identifying PE. The chest radiograph, when normal in a patient who is dyspnoeic, hints that PE is a diagnostic possibility. Among patients with PE and no prior cardiopulmonary disease a normal chest radiograph is found in 16% (Table 16.16.1.18). Atelectasis or a pulmonary parenchymal abnormality are the most frequent abnormalities present (68%). Pleural effusions are found in about one-half of cases and are usually small, with most limited to blunting of the costophrenic angle. In some studies, an elevated hemidiaphragm is the most frequent abnormality. Westermark’s sign (a prominent central pulmonary artery and decreased pulmonary vascularity) is identified by radiologists in only 7% of patients with PE. In cases of PE, those with a normal plain chest radiograph have the lowest pulmonary artery mean pressures. The highest pulmonary artery mean pressures are in patients with a prominent central pul- monary artery or cardiomegaly. Echocardiography Echocardiography

may show right ventricular dilatation and evi- dence of pulmonary hypertension, which—in the proper clinical setting—may strengthen the clinical impression that PE has oc- curred. Transoesophageal echocardiography sometimes may show proximal pulmonary emboli, but it has limited value in this regard. Arterial blood gases and alveolar–arterial oxygen difference A low partial pressure of oxygen in arterial blood (Pao2) is typical of acute PE and supports the diagnosis, but patients with acute PE can have a normal Pao2. Among patients with acute PE and no prior cardiopulmonary disease who have measurements of the Pao2 while breathing room air, 24% have a Pao2 of 80 mm Hg (10.5 kPa) or higher, and even among patients with submassive or massive acute PE, 12% have a Pao2 of this level or higher. A normal alveolar– arterial oxygen difference (alveolar–arterial oxygen gradient) does not exclude acute PE. No value of the alveolar–arterial oxygen dif- ference is diagnostic of PE, and no value can exclude the diagnosis. Other routine blood tests Among patients in whom a possible or definite cause for leuco- cytosis is eliminated, 80% of patients with PE have a normal white blood cell count, 6% a count of 10.1–11.9 × 109/litre, and 13% a count of higher than this. A white blood cell count of 20 × 109/litre or greater is rarely if ever seen. Leucocytosis is not more frequent in patients with the pulmonary haemorrhage/infarction syndrome than in other patients with acute PE. Biomarkers Cardiac troponin I (cTnI) and creatine kinase isoenzyme MB (CK- MB) are useful for assessment of prognosis in stable patients with acute PE who have right ventricular dilatation. Patients with a di- lated right ventricle have a mortality from PE of 13–29% if cardiac biomarkers are elevated, compared with 4% if they are not. Elevated biomarkers are not prognostically significant if right ventricular size is normal. Only a few patients with PE had an abnormal CK-MB, which limits its value if used as the only indicator of prognosis. Strategy for diagnosis With increasing severity of PE, from pulmonary infarction to iso- lated dyspnoea to circulatory collapse, trends suggest that the preva- lence of signs and symptoms increases, but generally recognized symptoms may be absent, even in patients with large pulmonary emboli. Clues that can assist the physician in assessing the possi- bility of PE, and avoiding inadvertent exclusion of the diagnosis are as follows: • Dyspnoea—onset is usually, but not always, within minutes or hours, and may be present only on exertion. Frequent in patients with large pulmonary emboli, but often absent in those with small pulmonary emboli • Orthopnoea—often present in dyspnoeic patients with PE • Circulatory collapse—may occur with PE in patients who do not have dyspnoea or tachypnoea or pleuritic pain • Tachypnoea—frequent in patients with large pulmonary emboli, but often absent in those with small pulmonary emboli • Crepitations (rales)—common among patients with pulmonary infarction, but less so in those with isolated dyspnoea or circula- tory collapse; they occur in those with radiographic evidence of a parenchymal abnormality • ECG—a normal ECG is frequent in patients with the pulmonary infarction syndrome, but uncommon in those with isolated dyspnoea; nonspecific ST-segment and T-wave changes are the most frequent abnormality • Chest radiograph—abnormalities are more common among pa- tients with pulmonary infarction but are often observed in those with isolated dyspnoea; patients with circulatory collapse may have a normal chest radiograph • Ventilation–perfusion scan—a high-probability interpretation occurs in a minority of patients with the pulmonary infarction syndrome but in the majority of those with the isolated dyspnoea syndrome; a low-probability scan may occur in patients with PE and circulatory collapse • Oxygenation—a Pao2 higher than 80 mm Hg (10.5 kPa) is not uncommon in patients with the pulmonary infarction syndrome, but such levels are uncommon in those with the isolated dyspnoea syndrome. Subjecting all patients who might have a PE to complex, expensive, and/or invasive tests is best avoided. Management algorithms have been developed to identify those at very low risk, who can then be Table 16.16.1.18 Chest radiograph findings in pulmonary embolism

in patients with no previous cardiac or pulmonary disease (n =117) Patients with radiographic finding (%) Atelectasis or pulmonary parenchymal abnormality 68 Pleural effusion 48 Pleural based opacity 3 Elevated diaphragm hemidiaphragm 24 Decreased pulmonary vascularity 21 Prominent central pulmonary artery 15 Cardiomegaly 12 Westermark's signa 7 a Prominent central pulmonary artery and decreased pulmonary vascularity. Data modified from Stein PD, et al. (1991). Clinical, laboratory, roentgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no pre- existing cardiac or pulmonary disease. Chest, 100, 598–603, with permission.

16.16.1 Deep venous thrombosis and pulmonary embolism 3725 spared imaging tests. These algorithms typically use scoring systems to stratify the clinical probability that the particular patient has a PE, proceeding to D-dimer testing of those a clinical probability that is not high. Untreated patients with a low or intermediate clinical probability by Geneva score or 'unlikely' clinical probability by Wells score and negative D-dimer by rapid ELISA or quantitative latex ag- glutination test had a 3-month incidence of PE of 0–0.4%. There was no fatal PE on follow-up. Patients with such a clinical probability and D-dimer need not to be investigated further. Patients with a high clinical probability and patients with an elevated D-dimer proceed to tests for the presence of pulmonary emboli, typically by contrast-enhanced spiral CT. Recommendations for the approach to the diagnosis of acute PE based on use of a pretest scoring system (Table 16.16.1.12) and D-dimer followed by imaging are discussed next. Recommendations for the diagnostic approach to patients in whom PE is not excluded by clinical assessment in combination D- dimer test depend on clinical probability, age, gender, pregnancy, the complexity of associated lung disease as determined from the plain chest radiograph, and the severity of illness. For patients with an elevated D-dimer and patients with a high- probability clinical assessment irrespective of the D- dimer, CT pul- monary angiography is recommended for most patients. If CT angiography is negative and clinical probability is low or intermediate, treatment is unnecessary, but a venous ultrasound is recommended if clinical assessment is intermediate or high prob- ability. In those with a high-probability clinical assessment and negative CT angiogram, additional options include serial venous ultrasound examinations, pulmonary scintigraphy, and pulmonary digital subtraction angiography. If CT angiography shows main or lobar pulmonary emboli, treat- ment is indicated irrespective of the clinical probability. With seg- mental or subsegmental pulmonary emboli the certainty of the CT diagnosis should be reassessed if clinical probability is low or inter- mediate, but treatment is indicated if the clinical probability is high. In those with segmental or subsegmental PE and a low or inter- mediate probability clinical assessment, pulmonary scintigraphy, a single venous ultrasound examination, or serial venous ultrasound examinations are optional. CT angiography should be repeated if image quality is poor. It appears safe to withhold treatment of isolated subsegmental PE provided that (1) pulmonary-respiratory reserve is good, (2) there is no evidence of DVT, (3) the major risk factor for PE was transient and no longer present, (4) there is no history of central venous cath- eterization or atrial fibrillation, and (5) the patient is willing and able to return for serial venous ultrasound examinations. Other considerations A venous ultrasound examination prior to imaging with CT angiog- raphy or prior to imaging with a ventilation–perfusion lung scan is optional and may guide treatment if positive. However, about 50% of patients with PE have negative noninvasive leg tests for DVT, even though DVT is the source of the PE. Scintigraphy as the first imaging test It may be that, with updated techniques, perfusion scintigraphy in a patient with a normal chest radiograph can provide diagnostic ac- curacy similar to CT angiography at a lower cost and with a lower radi- ation dose. Opinion is divided on whether perfusion lung scans or

CT angiograms should be obtained as a first imaging test in patients with a nearly normal chest radiograph. Some opt for perfusion imaging only if the patient is pregnant or young or has a contraindication to CT angiography, as with chronic kidney disease. Patients with emphy- sema, chronic obstructive pulmonary disease, or poorly controlled asthma may require a ventilation scan in addition to a perfusion scan even if the chest radiograph appears nearly normal. Some suggest use of the PISAPED criteria for interpretation. Some now favour the use of SPECT scintigraphy over planar ventilation–perfusion lung scans. Recommendations For women of reproductive age In women of reproductive age with a normal chest radiograph, if D-dimer is positive, most recommend either a perfusion lung scan as the first diagnostic test, or venous ultrasound to be followed by a perfusion lung scan. If the chest radiograph is abnormal, most rec- ommend a CT pulmonary angiogram. For patients who are pregnant Most investigators recommend venous ultrasound before imaging tests with ionizing radiation in patients who are pregnant. The European Association for Nuclear Medicine recommends a per- fusion scan without a ventilation scan, and a lower dose of radio- isotope. Others believe that rapid diagnosis is crucial and radiation is a secondary issue. If a CT pulmonary angiogram is performed, imaging should be strictly limited to the thoracic cavity, and low kVp, if applicable, should be utilized. For haemodynamically stable young men The effect of radiation on male reproduction is uncertain. In young men with a normal chest radiograph, opinions differ on which imaging test should be performed. In young men with an abnormal chest radiograph, most recommend CT pulmonary angiography as the first imaging test. For haemodynamically stable older men and women The risk of radiation-induced cancer is small with older men and women. Most recommend CT pulmonary angiography as the first imaging test in such patients, irrespective of whether the chest radio- graph is normal. Opinion differs, however, and scintigraphy is re- commended by many, particularly if the chest radiograph is normal. For patients with allergy to iodinated contrast material D-dimer with clinical assessment is recommended to exclude PE. Patients with mild iodine allergies may be treated with steroids prior to CT imaging. Venous ultrasound and pulmonary scintig- raphy are recommended as alternative diagnostic tests in patients with severe iodine allergy. Serial venous ultrasound is an option, as is gadolinium-enhanced CT angiography. For patients with impaired renal function D-dimer with clinical assessment is recommended to exclude PE. If further investigation is warranted, venous ultrasound is recom- mended, followed by treatment if positive, and pulmonary scintigraphy if venous ultrasound is negative. Serial venous ultrasound is an option if scintigraphy is nondiagnostic. However, as always it is a matter of balancing benefits and risks, and if the index of suspicion is high, then many physicians will proceed with CT pulmonary angiography.

section 16 Cardiovascular disorders 3726 For patients in extremis Bedside echocardiography in combination with bedside leg ultra- sonography are generally recommended as rapidly obtainable bed- side tests. In an appropriate clinical setting, either right ventricular enlargement or poor right ventricular function, or a positive venous ultrasound, can be interpreted as resulting from PE. Others recom- mend a portable perfusion scan or immediate transfer to an inter- ventional catheterization laboratory, but in many instances neither of these will be available. A combination of a negative bedside echo- cardiogram and venous ultrasound suggests that the patient may be in extremis for some other reason than PE, but the diagnosis of PE can be pursued with CT angiography, if this is feasible, and such imaging may be appropriate if and when the patient stabilizes. Serial noninvasive leg tests Instead of imaging the lungs, an alternative strategy for the diag- nosis of PE is to detect and treat DVT. Such a strategy can only be applied to patients with adequate cardiorespiratory reserve, because even a small recurrent PE might be dangerous if

reserve is poor. In practice this means obtaining serial ultrasonography of the legs over a period of 2 weeks, and treating if DVT is shown. Among patients with suspected PE who had a nondiagnostic ventilation–perfusion lung scan, and negative noninvasive leg tests (one study required low or intermediate probability clinical assessment and another normal cardiorespiratory reserve), PE at 3 months follow-up occurred in only 0.4% to 0.6%. However, most now believe that with many safe and accurate imaging options available, management on the basis of serial noninvasive leg tests is rarely (if ever) indicated. Treatment—general measures All patients who are hypoxic should be given supplementary oxygen at high concentration (enough to restore normal Pao2). In the early stages continuous monitoring of arterial oxygen tension by pulse oximetry is advised, with particularly careful clinical and arterial blood gas monitoring of those with coincident chronic chest disease in case CO2 retention is problematic. Resuscitation Patients with massive PE and circulatory collapse may look as though they are about to die, with cool peripheries, cyanosis, profound hypo- tension, and marked elevation of the jugular venous pulse. Features typical of long-standing pulmonary hypertension (palpable right ven- tricular heave, right ventricular gallop, loud P2, hepatomegaly, ascites, peripheral oedema) are unlikely to be present. This dramatic haemo-dynamic picture may not be simply due to the direct anatomical effects of occlusion of main pulmonary vessels (the same picture is not seen after pneumonectomy, when one pulmonary artery is tied off com- pletely), but also secondary to pulmonary neurogenic reflexes and local release of vasoactive substances, including 5-hydroxytryptamine and thromboxane from activated platelets. Every effort should be made to support the circulation until meas- ures designed to deal with the embolus (usually thrombolysis—see next) can be applied and take effect. Treatment—antithrombotic It is common and sensible practice to begin anticoagulant treat- ment as soon as the diagnosis of PE is suspected, unless there are serious concerns about the potential side effects of anticoagulation or imaging is immediately available. The antithrombotic regimen is the same as for DVT: see Table 16.16.1.8 and Chapter 16.16.2. Three direct oral factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) and one oral direct thrombin inhibitor (dabigatran)— were approved by the United States Food and Drug Administration (FDA) for treatment of venous thromboembolism (VTE). Some such drugs have also been approved for extended treatment (rivaroxaban, apixaban and dabigatran) or for prophylaxis (rivaroxaban and apixaban) following knee or hip replacement. Betrixaban, a direct factor Xa inhibitor, was approved for the prophylaxis of VTE in pa- tients hospitalized with an acute medical illness. None of these drugs requires monitoring of anticoagulant levels. They are as effective as conventional therapy with enoxaparin followed by a vitamin K an- tagonist in the treatment of DVT and PE. All of the novel oral anticoagulants have comparable rates of bleeding or less bleeding than treatment with a low-molecular-weight heparin/vitamin K antagonist. If bleeding occurs, the anticoagulant effect of the factor Xa inhibitors apixaban and rivaroxaban (but only these drugs) can be reversed with andexanet alfa. The anticoagulant effect of the direct thrombin inhibitor dabigatran can be reversed with idarucizumab. Resolution rate with anticoagulants Most patients (81%) treated with anticoagulants show complete CT angiographic resolution after 28 days, with emboli resolving at a faster rate in main or lobar pulmonary arteries than in segmental branches (Fig. 16.16.1.5). Among patients with no prior cardio- pulmonary disease who are treated with anticoagulants, resolution of 90% or more on perfusion lung scans is shown at 1 year in 91% of cases, compared with only 72% of those with prior cardiopul- monary disease. Thrombolytic therapy Thrombolytic therapy is not indicated for the routine treatment of PE. Hypotension, continuing hypoxemia while receiving high frac- tions of inspired oxygen (Fio2), and requirement for ventilatory Day 1 0 100 75 50 Resolution (%) 25 Days 2–7 Days 8–28

28 Days Main or lobar Segmental Fig. 16.16.1.5 Resolution of pulmonary emboli in main or lobar (▲) pulmonary arteries (PA) or segmental branches (●) according to number of days after initial CT angiogram. Bars = 95% confidence interval. Rate of resolution was slower in segmental branches. Data from Stein PD, et al. (2010). Resolution of pulmonary embolism on CT pulmonary angiography. AJR Am J Roentgenol, 194, 1263–8.

16.16.1 Deep venous thrombosis and pulmonary embolism 3727 support are indications for intervention. Analysis of data from 72 230 unstable (in shock or requiring ventilatory support) patients with PE throughout the United States of America from 1999 to 2008 showed that in-hospital mortality with thrombolytic therapy was 15% compared with 47% in those who did not receive thrombolytic therapy. Mortality was further reduced to 7.6% if a vena cava filter was used in addition to thrombolytic therapy compared with 33% mortality in those who received a vena cava filter, but no thrombo- lytic therapy. All-cause mortality in unstable patients was lower with thrombolytic therapy in every age group, including older people, irrespective of comorbid conditions. Right ventricular dysfunction on the echocardiogram of normo- tensive patients with PE may indicate impending haemodynamic instability. For this group meta-analysis showed mortality was 1.4% with thrombolytics versus 2.9% with anticoagulants, but this benefit was offset by major bleeding in 7.7% with thrombolytics, versus 2.3% with anticoagulants. A more rapid lysis of pulmonary thromboemboli occurs with thrombolytic agents than occurs spontaneously in patients treated only with anticoagulants, but pulmonary reperfusion as demonstrated on perfusion lung scans is similar after 2 weeks in patients treated with thrombolytic agents and patients treated with anticoagulants. In 1973 the Urokinase Pulmonary Embolism Trial showed no improvement of mortality and no difference of the rate of re- currence of PE among stable patients treated with thrombolytic therapy and patients treated with anticoagulants. There have been no subsequent prospective randomized trials to contradict these results, although a trend suggesting a lower rate of recurrent PE has been shown among patients with right ventricular dysfunction who were treated with tissue plasminogen activator. Thrombolysis has risks. Based on pooled data the frequency of major bleeding from tissue plasminogen activator among patients with PE in randomized trials was 14.7%. This occurred despite the fact that all studies excluded patients at a high risk of bleeding, such those with recent surgery, recent biopsy, peptic ulcer disease, blood dyscrasia, or severe hepatic or renal disease. The risk of intracranial haemorrhage with tissue plasminogen activator (2%) was higher among patients with PE than among patients who received tissue plasminogen activator for myocardial infarction. Even though there are risks of thrombolysis, mortality is lower in unstable patients (in shock or requiring ventilatory support) who receive thrombolysis than those who do not receive it. Regimens of thrombolytic therapy When thrombolytic therapy is appropriate, current evidence sup- ports a short (2-hour) infusion through a peripheral vein. The most widely used regimen In the United States is recombinant tissue plasminogen activator (rt-PA)(altelplase) 100 mg IV over 2 hours. In the United States, it is recommended that IV unfractionated hep- arin should be discontinued during the infusion of rt-PA.
• In Europe, rt-PA is administrated using a 10-mg bolus, followed by a 90-mg continuous IV infusion with concomitant unfractionated heparin. Inferior vena cava filters Recommendations for use of inferior vena cava filters are shown in Table 16.16.1.8. The Prévention du Risque d’Embolie Pulmonaire par Interruption Cave (PREPIC) study, a randomized controlled trial of permanent filters

plus anticoagulants (n = 200) compared with anticoagulants alone (n = 200) was performed in patients with proximal DVT, with or without symptomatic PE. Fewer patients in the filter group showed symptomatic PE at 1 year (1.1% versus 5.0%) and at 8 years 6.2% versus 15.1%) after recruitment. Recurrent DVT, however, was more frequent in the filter group and there was no difference in mortality. The Prévention du Risque d'Embolie Pulmonaire par Interruption Cave 2 (PREPIC2) trial was a randomized controlled trial of retriev- able filters in stable patients with acute pulmonary embolism. This trial showed no reduction of mortality in 200 stable patients with fil- ters compared with 199 who did not receive a filter. Subgroups that might benefit from filters could not be assessed. Such subgroups are

1. haemodynamically unstable patients (in shock or on ventilatory support) 2) require thrombolytic therapy and are stable, 3) undergo pulmonary embolectomy, 4) have solid malignant tumors (except liver gall bladder, bile ducts and ovary) and are >60 years old, 5) have chronic obstructive pulmonary disease and are >50 years old, 6) very elderly (>80 years) even though stable, and 7) patients who suffer re- current PE during the first 3 months (while on anticoagulants). These subgroups were shown to reduce in–hospital mortality based on ad- ministrative data from retrospective cohort studies of huge United States government or commercial databases. These results have not been assessed by randomized controlled trials and are not endorsed by authoritative guidelines. Routine insertion of an inferior vena cava filter is not indicated solely on the basis of a continuing predisposition for DVT, although in special circumstances this may be the best approach (e.g. in high- risk patients with DVT, severe pulmonary hypertension, and min- imal cardiopulmonary reserve). Several vena cava filters have been designed for percutaneous in- sertion and many are retrievable. They differ in outer diameter of the delivery system, maximal caval diameter into which they can be in- serted, hook design, retrievability, biocompatibility, and filtering effi- ciency. They may be effective alone in preventing PE, but anticoagulant therapy after insertion of a filter is recommended for the duration of treatment that would be required without a filter. Thereafter, anticoagu- lant therapy can be discontinued even though the filter remains in place. Complications of permanent vena cava filters include improper anatomical placement, filter deformation, filter fracture, insufficient opening of the filter, and filter migration; also perforation, thrombosis, and stenosis of the cava wall. Symptomatic occlusion of the inferior vena cava is the most frequent complication, occurring in about 9% of pa- tients. Complications at the site of insertion of the catheter do not differ from complications observed locally with other catheter techniques. DVT at the puncture site generally has been reported in 8% to 25%. Retrievable vena cava filters typically are successfully removed after 1 to 3 months, but some have been successfully removed after 1 year. PE after insertion of an inferior vena cava filter is uncommon (1%), and fatal embolism is rare. Possible mechanisms that can ex- plain PE after filter insertion are: (1) ineffective filtration, especially with tilting of the filter; (2) growth of trapped thrombi through the filter; (3) thrombosis on the proximal side of the filter; (4) filter mi- gration; (5) filter retraction from the caval wall; (6) embolization through collaterals; (7) embolization from sites other than the in- ferior vena cava; and (8) incorrect position of the filter. Over the last two decades, the use of inferior vena cava filters in the United States

section 16 Cardiovascular disorders 3728 of America has increased markedly in patients with PE, patients with DVT alone, and patients at risk who had neither PE nor DVT. The use for primary

prevention in patients who do not have DVT or PE has accelerated. Extensive use of permanent and retrievable vena cava filters indicates a liberalization of indications, but despite the benefits of retrievability, retrieval has been attempted in only a mi- nority of patients. For patients with retrievable IVC filters in whom the transient risk of PE has passed, the benefit/risk profile begins to favor filter removal between 29 and 54 days after insertion. Catheter interventions Catheter-tip devices for the extraction or the fragmentation of PE have the potential of producing immediate relief from massive PE. Such interventions may be particularly useful in patients in whom there is a contraindication to thrombolytic therapy. A suction-tip device for extraction of PE has been used in some patients, and thrombus fragmentation with a guide wire, angiographic catheter, balloon catheter, or specially designed devices has been reported in small case series or case reports. The release of fragmented thromboemboli into the distal pulmonary arterial branches is not a problem. A registry of management strategies used by hospitals throughout Germany showed use of catheter fragmentation in 1.3– 6.8% of patients with PE, depending on severity. Although originally it was thought that catheter embolectomy or fragmentation could substitute for thrombolytic therapy, it now appears to be an adjunct to thrombolysis, allowing a larger surface area of the fragmented emboli to be exposed to thrombolytic agent. Among patients who undergo fragmentation with standard angio- graphic catheters, the rate of successful clinical outcome with a local infusion of thrombolytic agents in combination with fragmentation is higher than with a systemic infusion. Pulmonary embolectomy Thrombolytic therapy is likely to give better results than embol- ectomy, although the latter may have life-saving potential in some instances. The average operative mortality in the United States of America among 620 unstable patients operated from 2004 to 2008 was 40%, and among 1550 stable patients, mortality was 23%. These data reflect average results. Advanced centres with expertise might show a lower mortality. A candidate for pulmonary embolectomy should meet the following criteria: (1) massive PE, angiographic- ally documented if possible; (2) haemodynamic instability (shock) despite heparin therapy and resuscitative efforts; and (3) failure of thrombolytic therapy or a contraindication to its use. Chronic pulmonary thromboembolic hypertension The vast majority of PE resolve because of natural thrombolytic pro- cesses. Residual emboli, if any, undergo fibrovascular organization causing chronic obstruction to pulmonary arterial blood flow. It is estimated that 2.8% of patients with PE develop chronic thrombo- embolic pulmonary hypertension, usually within 3 years after the acute PE. The predominant symptom of chronic thromboembolic pulmonary hypertension is unexplained dyspnoea on exertion, often following an asymptomatic period of several months or years after the acute PE. The reference standard for the diagnosis is com- bined right heart catheterization to quantify the haemodynamic im- pairment, and conventional pulmonary angiography to determine the extent and proximal location of the chronic thromboembolic obstruction. CT pulmonary angiography is essential to exclude rare conditions that may present with similar signs and symptoms such as fibrous mediastinitis, mediastinal carcinoma, and pulmonary artery sarcoma. Pulmonary thromboendarterectomy in an experienced centre is the treatment of choice in symptomatic patients with surgically ac- cessible thromboemboli. Early diagnosis is important because the surgical mortality in patients who have progressed to dyspnoea at rest is substantially greater than among those with less severe symp- toms. Neither anticoagulants nor vasodilators are effective, with the haemodynamic and symptomatic benefits of medical therapy being modest in comparison to those resulting from successful pulmonary thromboendarterectomy. See Chapter 16.15.2 for further discussion. FURTHER READING Agnelli G, Becattini C (2010). Acute pulmonary embolism. N Engl J Med, 363, 266–74. Agnelli G, et al. (2013). AMPLIFY Investigators: oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med, 369, 799–808. Chatterjee S, et al. (2014). Thrombolysis for pulmonary embolism and risk of all-

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