

PULMONARY EMBOLISM

Pathophysiology

Pulmonary emboli most often arise from the deep veins of the lower extremity and pelvis and very rarely from subclavian or arm veins. Their consequences become apparent when more than 30-50% of the pulmonary arterial bed is occluded. In addition to obstruction, acute PE leads to the release of pulmonary artery vasoconstrictors and hypoxemia, with a subsequent increase in pulmonary vascular resistance and right ventricular afterload, RV dilatation and tricuspid regurgitation.¹ RV pressure overload can also lead to interventricular septal flattening and deviation toward the left ventricle in diastole, thereby impairing LV filling. The subsequent reduction in coronary artery perfusion pressure in the context of the increased wall stress leads to RV ischemia and subsequent failure. The prevalence of acute RV failure in the setting of acute PE ranges from 25% to 60%, and predictors of RV dysfunction include >50% of the pulmonary artery tree occluded by thrombus.² Ventilation to perfusion mismatch, increases in total dead space, impaired transfer of carbon monoxide due to loss of gas exchange surface, and decreased pulmonary compliance caused by lung edema, result in arterial hypoxemia and an increased alveolar-arterial oxygen gradient. Hyperventilation may contribute to hypocapnia and respiratory alkalosis. The presence of hypercapnia suggests massive PE leading to increased anatomic and physiological dead space and impaired minute ventilation.^{1,3}

Presentation

The presentation of PE ranges from mild dyspnea to cardiogenic shock, thus making the disease difficult to diagnose. Dyspnea is the most common symptom and tachypnea the most common physical sign. Patients may be anxious but otherwise completely asymptomatic or present with hypotension and cyanosis. Ventricular arrhythmias are very rare.⁴ Pleuritic pain, cough or hemoptysis indicate pulmonary infarction by a peripherally located PE. Nearly 25% of the cases present with sudden death.³ Patients may also be asymptomatic.

Diagnosis

Pulmonary embolism should be suspected in all patients who present with new or worsening dyspnea, chest pain, or sustained hypotension without an alternative obvious cause, but the diagnosis is confirmed by objective testing in only about 20% of patients.⁵ Clinical prediction scores⁶⁻⁸ and diagnostic criteria are presented in Tables 1 and 2, and Figure 1. The simplified Wells and Revised Geneva rules are easier to use and appear to have the same accuracy as the original ones. When the probability of PE is low, the

Pulmonary Embolism Rule-Out Criteria (PERC) can be used for ruling out PE without testing (Table 1).⁹

Chest X-ray is usually normal. Findings such as focal oligemia (Westermarck sign), a peripheral wedge-shaped opacity, usually in the lower half of the lung field (Hampton's hump), or an enlarged right descending pulmonary artery (Pallas's sign) are rare.³

The **ECG** may reveal signs of RV strain, including incomplete or complete RBBB, T-wave inversion in the anterior precordium, and an S wave in lead I, and a Q-wave and T-wave inversion in lead III (the S1Q3T3 patterns), or may mimic an old inferior MI. ST elevation may also be seen in the inferior leads due to RV strain.¹⁰ ECG may be also be normal, especially in the young.

Echocardiography is insensitive for diagnosis but the detection of RV dysfunction is an ominous prognostic factor (Figure 2, and Table 3)). Regional RV dysfunction with free wall hypokinesia sparing the apex (*McConnel sign*) is specific for PE, but seen with massive emboli.³

D-dimer ELISA can be used to exclude PE in patients with a low suspicion of PE. D-dimer is a degradation product of fibrin that is also produced in a wide variety of conditions such as cancer, inflammation and dissection of the aorta, and pregnancy. The test is therefore of limited value in high probability of PE, because comorbid conditions may have already raised the D-dimer levels. The specificity of the test is also reduced in hospitalized or elderly patients. The usually accepted threshold level is 500 ng/mL, but an age-adjusted d-dimer cut-off, defined as age x 10 in patients 50 years or older, appears to be more appropriate.^{11 12} The sensitivity of the assay used should be always taken into account when interpreting D-dimer results. The clinical pretest probability is also important. PE is ruled out by a by a D-dimer level < 500 ng/mL in patients with a moderate pretest probability (Wells score 4.5-6), but can also be ruled out in patients with a low clinical pretest probability (Wells score, 0-4) and D-dimer level < 1000 ng/mL.¹³

CT pulmonary angiography with a multidetector scanner (CTPA) and the use of intravenous contrast is the principal diagnostic imaging modality with a negative predictive value 95-99% (Tables 4-6).^{3,5,14} The YEARS diagnostic algorithm may result in a 14% decrease of CT pulmonary angiography in all ages.⁸ In patients with a high clinical probability of pulmonary embolism and negative findings on CTPA, the value of additional testing is controversial. Venous ultrasonography shows a deep-vein thrombosis in less than 1% of such patients.⁵ CTPA is considered at least as accurate as invasive pulmonary angiography.³ Isolated subsegmental PE can be detected in up to 9% of patients subjected to CTPA, whereas incidental discovery of clinically unsuspected PE occurs in 1-2% of all thoracic CT examinations. The proper management of these cases is not established.¹⁵ Magnetic resonance imaging is less sensitive.¹

Venous ultrasonography (compression ultrasonography), that has now replaced venography, should precede imaging tests in pregnant women and in patients with contraindication to CT scanning. Confirmed DVT in patients with suspected PE is an indication for anticoagulation therapy.⁵

Magnetic resonance venography may have a role in specific populations such as morbidly obese patients where compression ultrasonography is not feasible.¹⁶

Ventilation perfusion (V/Q) scans are reserved for patients with renal failure allergy to contrast dye, or when a multidetector CT scanner is not available.¹² A normal scan rules out a PE but is diagnostic in only 20-50% of patients with suspected PE.⁵ MCT delivers a higher dose of radiation to the mother but a lower dose to the fetus than ventilation-perfusion lung scanning. Single photo emission tomography ventilation perfusion (SPECT V/Q) is a promising new modality with better sensitivity than planar V/Q.¹⁷ V/Q single-photon emission CT is an emerging technology with potential diagnostic accuracy similar to CT angiogram in acute PE without using intravenous contrast.¹⁶

Risk Stratification

The average 30-day mortality risk for PE patients is 31%.¹⁸ Patients treated with anticoagulation of thrombolysis have an early mortality of 3-15%.¹⁹

Shock and sustained hypotension indicate an in-hospital mortality of 58% (ICOPERegistry).

²⁰ Risk stratification schemes are presented in Tables 6-12, and Figure 4). In stable patients, the simplified version of the Pulmonary Embolism Severity Index (**sPESI**) is a practical way for risk stratification of patients with diagnosed PE (Table 7).²¹ The **Hestia** Rule is an alternative. Using these tools, more than one third of patients with PE can be treated at home.²² A new multimarker calculator also improved the risk stratification for mortality beyond that of the ESC model.²³

RV dysfunction detected on echocardiography or MCT (RV diameter/LV diameter >0.9) is an independent predictor of mortality,²⁴ and RV pressure overload and dysfunction on imaging possesses a prognostic value comparable to the elevation of cardiac troponins or natriuretic peptides.²⁵ RV failure with hemodynamic compromise is encountered in <5% of all patients with acute PE, and is associated with an at least 15% risk of in-hospital death within the first hours after admission.²⁶ RV dysfunction assessment, mainly by BNP/NT-proBNP or echocardiography, has been shown to improve identification of low-risk patients that may be candidates for outpatient management or short hospital stay.²⁷

BNP and **pro-BNP** elevated levels as well as **troponins** indicate an adverse outcome, especially in the context of echocardiographic RV dysfunction.^{28,29} High-sensitivity troponin (hsTnT cutoff level of 14 pg/mL) exhibits a high prognostic sensitivity for excluding early

PE-related death, and combination of hsTnT with the sPESI improves the prediction of both acute and long-term outcome.³⁰

Classification of PE

Massive PE

Acute PE with sustained hypotension (systolic blood pressure < 90 mm Hg for at least 15 minutes or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction, pulselessness, or persistent profound bradycardia (heart rate < 40 bpm with signs or symptoms of shock)).^{17 31}

Submassive PE

Acute PE without systemic hypotension (systolic blood pressure < 90 mm Hg) but with either RV dysfunction or myocardial necrosis.

RV dysfunction is defined by the presence of at least 1 of the following:

- RV dilation (apical 4-chamber RV diameter divided by LV diameter > 0.9) or RV systolic dysfunction on echocardiography
- RV dilation (4-chamber RV diameter divided by LV diameter > 0.9) on CT
- Elevation of BNP (>90 pg/mL) or of N-terminal pro-BNP (>500 pg/mL)
- Electrocardiographic changes (new complete or incomplete RBBB, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)

Myocardial necrosis is defined as elevation of troponin I (>0.4 ng/mL) or of troponin T (>0.1 ng/mL)

Low risk PE

Acute PE and the absence of the clinical markers of adverse prognosis that define massive or submassive PE.

Classifications by the ESC and AHA/ACC are presented in Table 9 and Figure 5.

Acute Therapy

Hemodynamically stable patients

Anticoagulation

Acute pulmonary embolism requires initial short-term therapy with **heparin (UFH or LMWH) or fondaparinux** for at least 5 days, followed by therapy with a vitamin K antagonist for at least 3 months, depending on the risk of recurrence. In patients with a high clinical probability of pulmonary embolism, anticoagulant treatment should be initiated while diagnostic confirmation is awaited. LMWH are at least as efficacious and safe as UFH.³² Dose adjustment is needed in renal failure (see UA/NSTEMI). Fondaparinux is also efficacious and

safe compared to UFH,³³ and may be used in heparin-induced thrombocytopenia (although not approved for this purpose), but is contraindicated in patients with a creatinine clearance <30 ml/min. UFH is preferable in thrombolysis due to its short half-life (1.5 h compared to 3-4 h and 17-21 h for LMWH and fondaparinux, respectively) and possibility of immediate reversal, and in patients with creatinine clearance <30 ml/min.

The risk of major bleeding with these agents is 3-6%. For heparin-induced thrombocytopenia see Chapter on ACS Therapy.

- UFH: IV bolus 80 iu/kg (or 5000 iu), followed by continuous infusion 18 iu/Kg/h (or 1,000 iu/h) aiming at aPTT 1.5-2.5 control (measured 4-6 h after bolus and 3 h after each dose adjustment).
- Enoxaparin: 1mg/kg/12 h SC (or 1.5 mg/kg/24 h in the USA)
- Fondaparinux: 5 mg SC (body weight <50 mg)
 - 7.5 mg SC (body weight 50-100 kg)
 - 10 mg SC (body weight > 100 kg)

Other LMWH such as dalteparin (100 IU/Kg /12 h or 200 IU/Kg/24 H) may also be used.

Stable, low-risk patients, might be managed on an out-patient basis after the with discharge <or= 24 h after diagnosis and instructions on self-performed SC injections,³⁴ but more data is certainly needed.

Vitamin K antagonists are given at the first day of IV/SC anticoagulation with a target of INR 2-3. In patients with pulmonary embolism secondary to a temporary (reversible) risk factor, therapy with vitamin K antagonists should be given for at least 3 months. The risk of recurrent pulmonary embolism is less than 1% per year on anticoagulation and 2 to 10% per year after the discontinuation of such therapy.⁵ Thus, the duration of long-term anticoagulation (a minimum of 3-6 months) should be based on the risk of recurrence after cessation of treatment with vitamin K antagonists and the risk of bleeding during treatment.³⁵ Male sex, proximal DVT, elevated-D dimer levels after discontinuing anticoagulation,³⁶ as well as cancer, inherited thrombophilia (factors V and II-Table), obesity and unprovoked pulmonary embolism indicate candidates for indefinite anticoagulation with periodic reassessment of the risk-benefit ratio. An INR of 2.0-3.0 is recommended during the first 3 to 6 months after the acute event. After an initial course, low-intensity therapy (INR 1.5-1.9) may be an option.³⁷

The **new oral anticoagulants** are antithrombin (factor IIa) or factor Xa inhibitors, and offer a safe alternative to warfarin without the need for monitoring.³⁸ They are all now approved by the FDA for PE and DVT. The oral antithrombin **dabigatran** at a dose of 150 mg bd has been shown not inferior to warfarin in patients with PE or deep vein thrombosis, with reduced risk of bleeding in patients already having received heparin for 5-111 days (RE-COVER and RE-COVER II trials).^{39,40} The short-acting oral Xa inhibitor **rivaroxaban** (15 mg twice daily for 3

weeks, followed by 20 mg once daily without initial heparin) was recently found to treat equally well PE compared to enoxaparin followed by a vitamin K antagonist, albeit with less bleeding risk (EINSTEIN-PE and EINSTEIN -DVT trials).⁴¹ **Apixaban** (10 mg bd for 7 days, followed by 5 mg bd for 6 months without initial heparin) was equally effective to conventional therapy (subcutaneous enoxaparin, followed by warfarin), but with significantly less bleeding in patients with PE or DVT (AMPLIFY trial).⁴² Apixaban was also noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding (Caravaggio trial).⁴³ In a recent meta-analysis, the UFH-vitamin K antagonist combination was the least effective strategy, while rivaroxaban and apixaban alone were associated with the lowest risk for bleeding.⁴⁴ The risk of bleeding has been found significantly lower with apixaban than with rivaroxaban (COBRA RCT).⁴⁵ **Edoxaban** (60 mg od, or 30 mg od in patients with creatinine clearance 30-50 ml/min or a body weight <60 kg) after initial treatment with heparin was also noninferior to warfarin and caused significantly less bleeding (HOKUSAI-VTE trial).⁴⁶

NOACS may also be used in patients with cancer but there is a higher risk of bleeding in patients with GI and urologic malignancies.⁴⁷ There is currently insufficient evidence to support the use of NOACs in patients with antiphospholipid syndrome, heparin-induced thrombocytopenia, or venous thrombosis at unusual sites, such as splanchnic vein thrombosis.¹⁶

Statin therapy decreases the risk of recurrent PE, irrespective of anticoagulation.⁴⁸

Recent data suggest that anticoagulation should be restarted following discharge after an **episode of GI bleeding**, especially in patients with malignancy.⁴⁹ However, this study was small, and although a trend towards more bleeding in the anticoagulated group was not statistically significant, this could represent a type II error due to a small sample size.

Validated triage tools such as Hestia or sPESI in combination with a negative clinical judgement can be used in the emergency department to select acute PE patients for **home treatment**.⁵⁰

Recommendations are summarised in Tables 13-15, and Figures 6-8.

Inferior vena cava filters

They are recommended only in patients in whom anticoagulation is absolutely contraindicated (Table 16).¹⁶ In general, may reduce the risk of subsequent PE but increase the risk of DVT, and effects on mortality are controversial mortality,^{51,52} with suggestions that may even increase it.⁵³ In patients who cannot take anticoagulants due to a significant bleeding risk, inferior vena cava filter insertion is associated with a lower risk of PE-related death but a higher risk of recurrent VTE and DVT.^{54 55} Early prophylactic placement of a vena cava filter after major trauma did not result in a lower incidence of symptomatic pulmonary embolism or death at 90 days than no placement of a filter.⁵⁶

Retrievable vena cava filters are preferable, since permanent vena cava filters increase the risk of DVT.⁵⁷

Fibrinolysis

Fibrinolysis confers no benefit over conventional anticoagulation in stable, low-risk patients with PE.¹⁵ However, in hemodynamically stable patients with right ventricular dysfunction, thrombolytic therapy is associated with lower rates of all-cause mortality and increased risks of major bleeding and intracranial haemorrhage (especially in patients >65 years of age).^{58 59} In intermediate-risk, normotensive patients, fibrinolysis with tenecteplase and heparin has also conferred a reduction in death or hemodynamic collapse at 7 days, but at a significant excess in hemorrhagic stroke, especially in those ≥ 75 years old (PEITHO trial).^{60,61} Thus, intermediate-risk patients should receive fibrinolysis only if they decompensate. An alternative strategy in normotensive patients might consist of reducing by 50% (or even more) the dosage of the thrombolytic agent used.¹⁵ **Streptokinase** (250,000 iu over 30 min, followed by 100,000 iu/h over 12-24h or preferably 1.5 million iu over 2h), **urokinase** (4400 iu/kg over 10 min, then 4400 iu/kg/h over 12-24, or 3 million iu over 2h), and **alteplase** (tPA, 100 mg over 2h or 0.6 mg/kg over 15 min up to 50 mg) are the approved agents, but **rateplase** and **tenecteplase** may also be used. UFH heparin is discontinued before thrombolysis and restarted when the aPTT is <80 sec, but it can be continued with the direct plasminogen activators alteplase, rateplase or tenecteplase. All thrombolytics should be given intravenously, since direct administration into the pulmonary artery has not been found superior. The greatest benefit is observed when treatment is initiated within 48 h of symptom onset, but thrombolysis can still be useful in patients who have symptoms for 6-14 days. A rate of 9.9% major bleeding and 1.7% death or intracranial hemorrhage has been reported in recent trials.⁵⁹ Contra-indications to thrombolysis such intracranial disease, uncontrolled hypertension, ischemic stroke in previous 6 months, major surgery or trauma within the last 3 weeks, and gastrointestinal bleeding within the last month are discussed in the Chapter on ACS Therapy.

Pharmacomechanical therapy

Catheter-based therapies (including catheter-directed thrombolysis and mechanical thrombectomy) may be beneficial in patients hospitalized with intermediate- or high-risk pulmonary embolism.⁶² Low-dose, local fibrinolysis combined with thrombus fragmentation or aspiration may also be used in massive, centrally located thrombi. Ultrasound accelerated thrombolysis via the EkoSonic catheter is a new option for patients with at least 1 main or lower lobe pulmonary artery and echocardiographic RV/LV ratio ≥ 0.9 -1. In the first randomised trial to test catheter intervention (ULTIMA) a fixed-dose, catheter-directed, ultrasound-assisted thrombolysis regimen (10 mg recombinant tissue plasminogen activator per treated lung over 15 hours) was superior to anticoagulation alone in the reversal of RV

dilatation in intermediate-risk patients.⁶³ In the HEI-PEITHO RCT, in patients with acute, intermediate-risk pulmonary embolism, ultrasound-facilitated, catheter-directed fibrinolysis plus anticoagulation led to a lower risk of the composite of pulmonary embolism-related death, cardiopulmonary decompensation or collapse, or symptomatic recurrence of pulmonary embolism within 7 days than anticoagulation alone.⁶⁴ Ultrasound causes reversible disaggregation of uncrosslinked fibrin fibers which may increase the thrombus permeability for thrombolytic drugs. Major bleedings, in particular intracranial haemorrhages, seem to be less frequent with this treatment regimen than with systemic thrombolysis.⁶⁵ Computer-assisted vacuum thrombectomy (CAVT) is a recently developed endovascular therapy that uses an algorithm from a microprocessor designed to quickly detect and remove thrombus. In the STORM-PE RCT, CAVT and anticoagulation resulted in a significantly greater reduction in right ventricular/left ventricular ratio at 48 hours compared with anticoagulation alone, with comparably low rates of major adverse events in both treatment arms, in patients with intermediate-high risk PE.⁶⁶ Large-bore mechanical thrombectomy is associated with significantly better outcomes compared with catheter-directed thrombolysis.⁶⁷

Hemodynamically unstable patients

They should be treated with primary reperfusion (Figure 9, and Tables 17-20). Pharmacological or mechanical fibrinolysis may be used. Fibrinolysis should be considered even in the presence of an increased risk of bleeding, such as after recent surgery or trauma (except for those affecting the central nervous system), especially, if surgical embolectomy or catheter-directed treatment is not immediately available.¹⁵

Modest fluid challenge (500 ml dextran) may increase cardiac index. Aggressive volume expansion may worsen RV function. Nasal oxygen should be given for hypoxia.

If mechanical ventilation is necessary, positive end-expiratory pressure should be applied with caution since it may worsen RV failure.

Dobutamine and **epinephrine** in case of hypotension are the agents of choice if inotropic support is needed.³ Cardiac index should not be raised above physiological values without proper reperfusion therapy since this may aggravate the ventilation-perfusion mismatch.

Fibrinolysis offers a 59% reduction in mortality and is clearly indicated in patients with hemodynamic instability.⁵⁹ Percutaneous mechanical thrombectomy (thrombus fragmentation and aspiration) and surgical embolectomy are offered to high-risk patients with contraindication to thrombolytic treatment and those in whom thrombolytic treatment has not improved hemodynamic status.

Percutaneous mechanical thrombectomy confers a clinical success in approximately 87% of cases at a rate of major procedural complications of 2.4%.^{62,68,69}

Four main categories exist:

1. Catheter-directed, ultrasound-assisted thrombolysis.
2. Aspiration thrombectomy through a dedicated suction catheter.
3. Thrombus fragmentation through a balloon, manually rotating pigtail, or a dedicated device.
4. Rheolytic thrombectomy through high-velocity jet suction catheters.
5. Computer-assisted vacuum thrombectomy.

Surgical embolectomy may be now performed off bypass and without aortic cross-clamping with a <10% intraoperative mortality in experienced centers. It is indicated in patients with massive PE and contraindications to fibrinolysis who have surgically accessible, centrally located PE.^{31 70}

Extended Therapy

The cumulative 2-year incidence of chronic thromboembolic hypertension following PE is 2.3%, while the incidence of clinical, echocardiographic or laboratory abnormalities indicating pulmonary hypertension and/or RV dysfunction is 16%.⁷¹ Apart from the known risk factors for VTE, additional risk factors for recurrences are proximal or multiple PEs, residual vein thrombosis after anticoagulation, abnormal D-dimer after cessation of anticoagulation.⁷² Indications of extended anticoagulation beyond the initial 3 months of therapy are presented in Tables 21-24. However, patients with a first unprovoked VTE have a high risk of recurrence of VTE (10% after 1 year and 30% at 5 years) and should therefore receive indefinite therapy unless bleeding risk is high.^{16 73} The risk in men is at least double that in women. Serially measured D-dimer levels and HERDOO2 clinical decision rule can guide discontinuation of extended anticoagulation in female patients.¹⁶ Women with <2 of the following criteria have a low risk of recurrent VTE: signs of post-thrombotic syndrome in either leg (hyperpigmentation, edema, or redness), a D-dimer level ≥ 250 $\mu\text{g/L}$ while taking an anticoagulant 6 months after initiation of treatment, obesity with body mass index ≥ 30 , and older age, ≥ 65 years.⁷⁴ The VTE-PREDICT risk score can be used to predict recurrent venous thromboembolism and bleeding with extended anticoagulation.⁷⁵ In patients with provoked VTE, low-intensity therapy with apixaban (2.5 mg bd) for 12 months resulted in a lower risk of symptomatic recurrent VTE than placebo, with a low risk of major bleeding (HIPPON RCT).

A, a new oral anticoagulant or warfarin in patients with mechanical valves or several kidney disease may be used.³⁸ Following warfarin therapy for 3-6 months, **aspirin** administration reduces the overall risk of recurrence by more than a third in patients with a first unprovoked VTE, without significantly increasing the risk of bleeding.⁷⁶⁻⁷⁸ In patients

who had already completed a 3-month course of anticoagulation with either warfarin or dabigatran, continuation of **dabigatran** 150 mg bd up to 36 months was as effective and carried a lower risk of bleeding than warfarin, although there was increased incidence of acute coronary syndromes (RE-MEDY, RE-SONATE trials).⁴⁰ Extended anticoagulation with **rivaroxaban** 20 or 10 mg od (EINSTEIN-CHOICE),⁷⁹ or **apixaban** 2.5 for up to 12 months appears beneficial.^{80,81} In patients with cancer and acute low-risk pulmonary embolism of the simplified version of the Pulmonary Embolism Severity Index score of 1, 18 months are superior to 6 months of **rivaroxaban** treatment (ONCO PE).⁸²

Sulodexide, a heparin sulfate containing glycosaminoglycan with antithrombotic properties has also been found safe and effective for 2 years following 3-12 months anticoagulant therapy for VTE.⁸³ In elderly patients on anticoagulation, a high level of physical activity is associated with a decreased risk of major bleeding.⁸⁴ IVC filters are not indicated in patients who can receive anticoagulation following an acute PE associated lower extremity venous thrombus.⁸⁵

Prevention of VTE

Apart from high-risk patients who may need long-term anticoagulation after an episode of PE, VTE prevention in the absence of a previous episode, may also be necessary in several clinical settings. **Heparin**, **LMWH** or **UFH**, is used for thromboprophylaxis of VTE in surgical and medical hospitalized patients. When used for thromboprophylaxis in ill medical patients, **rivaroxaban** (10 mg daily) has produced controversial results. It reduced the risk of venous thromboembolism but with an increased risk of bleeding compared to enoxaparin 50 mg SC (Magellan trial),⁸⁶ but was not superior to placebo (Mariner trial).⁸⁷ **Apixaban**, 2.5 mg po bd for 30 days, was not superior to enoxaparin, 40 mg SC od for 6-14 days, and was associated with significantly more major bleeding events.⁸⁸ **Edoxaban**, 60 mg od for 6-12 months reduced cancer-associated thromboembolism more than dalteparin but at a higher rate of major bleeding.⁸⁹ The American College of Physicians (ACP) recommends pharmacologic prophylaxis with LM or UF heparin or a related drug in medical (including stroke) patients, and against the use of mechanical prophylaxis with graduated compression stockings for prevention of venous thromboembolism.⁵⁷ **FXI-ASO**, an anitise oligonucleotide that specifically reduces factor XI levels has been found equivalent to enoxaparin in preventing DVT after knee arthroplasty.⁹⁰ Postoperative factor XIa inhibition with oral **milvexian** in patients undergoing knee arthroplasty was also effective for the prevention of venous thromboembolism and was associated with a low risk of bleeding (AXIOMATIC-TKR RCT).⁹¹ In patients with extremity fractures that had been treated operatively or with any pelvic or acetabular fracture, thromboprophylaxis with aspirin, 81 mg bd, has been found

noninferior to low-molecular-weight heparin in preventing death and was associated with low incidences of deep-vein thrombosis and pulmonary embolism and low 90-day mortality.⁹² Intensive therapy lipid lowering may also be beneficial in preventing VTE.⁹³

Special Conditions

Thromboembolism in Cancer

General recommendations for the management of VTE in patients with cancer are provided in the Chapter on Cardio-oncology. Tables 24 and 25 also present recommendations.

In patients with a PE, extended-duration anticoagulant therapy may be recommended but care is needed because there is also an increased risk of bleeding.⁹⁴

Thromboembolism in Pregnancy

Pregnant women have a 4 to 5-fold increased risk of thromboembolism compared with non-pregnant women, and PE is a leading cause of mortality in pregnancy in developed countries.⁹⁵ The diagnosis of PE is challenging because the presentation often overlaps with symptoms common during normal pregnancy (Tables 26-28, and Figures 10-12).^{96,97} The risk is higher in the postpartum period, particularly after a caesarian section. Women are hypercoagulable for the first 6 weeks postpartum, but the risk levels off after 12 weeks.⁹⁸ Thus, following delivery, thrombotic prophylaxis should be considered for 12 weeks in patients with risk factors, and estrogen-containing contraception in patients without risk factors should be withheld for 12 weeks. Approximately 80% of thromboembolic events in pregnancy are venous with a prevalence of 0.5-3/1,000 pregnant women. Compression ultrasonography of the proximal veins should be considered when new-onset deep venous thrombosis is suspected. When using anticoagulants, heparin compounds are preferred. In suspected PE the usefulness of D-dimer is controversial since they physiologically increase during pregnancy. The danger threshold for foetal damage is 50 mSv (50000 mGy), thus a V/Q scan is preferable to CT.

PE in Heart Failure

The relative risk of PE doubles in patients with heart failure.⁹⁹ Diagnosis may be difficult and is based on the presence of dyspnea and hypoxemia out of proportion to findings of vascular congestion, new or worsened right greater than left heart failure (especially high JVP in the absence of pulmonary rales), and demonstration of new or worsened RV dilatation and dysfunction on echocardiography or chest CT. Elevated biomarkers and D-dimers are of no help. Oral anticoagulation is more difficult to manage due to stasis and concomitant medications (amiodarone and clopidogrel potentiate the effect of warfarin, whereas spironolactone accelerates its metabolism. VTE prophylaxis with stockings, pneumatic compression devices or LMWH or warfarin is indicated in all hospitalized patients with heart

failure.⁹⁹

Chronic Kidney Disease

Patients with CKD are at an increased risk of developing VTE, including deep vein thrombosis and pulmonary embolism. In patients with nephrotic syndrome, risk of VTE is particularly high and requires expert nephrological consultation.

Recommendations for therapy of VTE are provided in Table 29 and Figure 13.

Right Heart Thrombi

Thrombolysis is also indicated in the presence of right heart thrombi (in <4% of patients with PE), although surgical embolectomy may be required in the presence of massive thrombi, especially those straddling the interatrial septum through the foramen ovale. Conventional anticoagulation is not effective.

Non-thrombotic PE

Air embolism may occur during catheterization procedures. Hemodynamic consequences depend on the amount injected. Nasal oxygen is the treatment of choice. *Fat* embolism occurs after fracture of long bones and, rarely, with liposuction, lipid and propofol infusions, and hepatic necrosis. *Septic, tumor, and talk* (drug abusers) emboli may also occur. Amniotic fluid embolism is rare but potentially catastrophic (1/8000-1/80000 pregnancies). Treatment is supportive.

Follow-up

The management of persistent symptomatology is presented in Table 30 and Figures 14 and 15. Risk factors and predisposing conditions for chronic thromboembolic pulmonary hypertension are presented in Tables 31 and 32. Recommendations for follow-up in general are presented in Tables 33 and 34.

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