

Review Article

Managing pulmonary embolism from presentation to extended treatment



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ABSTRACT

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

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

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Introduction

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

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

Presentation and Diagnosis of Primary Pulmonary Embolism

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

1. Sudden death

The 1-day survival rate after PE (64%) is much lower than after DVT (97%), and the 7-day survival rate is also poor (59%) [9]. A non-specific clinical presentation [10] means that a definite diagnosis is often established only at autopsy in patients who die of PE [11].

2. Typical clinical presentation

In line with previous observations [12,13], a recent Italian survey found that the most common clinical symptoms of PE were dyspnoea (78–81%), pleuritic chest pain (39–56%) and fainting or syncope (22–26%) [14]. These are present individually or in combination in 90% of confirmed cases [10]. Isolated rapid-onset dyspnoea is usually attributable to the haemodynamic consequences of central PE. Pleuritic chest pain is frequent and results from pleural irritation, in which proximal or distal emboli cause pulmonary infarction and alveolar haemorrhage, sometimes with haemoptysis. Syncope, indicative of a severely reduced haemodynamic reserve and, in the most severe cases, shock and arterial hypotension, can also be present [10].

Clinical signs of PE lack sensitivity and specificity. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study found that tachypnoea (≥ 20 breaths/min) and tachycardia (> 100 beats/min) were significantly more common in confirmed PE than in cases where PE was excluded (57% vs. 47% and 26% vs. 16%, respectively; $P < 0.01$) [15], whereas PIOPED I and another study found only small differences [12,13]. All of these studies found signs of DVT in more patients with confirmed PE than in those without PE (47% vs. 23% with calf or thigh involvement in PIOPED II; $P < 0.001$) [12,13,15].

3. Atypical clinical presentation

Cough, substernal and pleuritic chest pain, haemoptysis and wheezing occurred in up to 59% of confirmed PE cases in PIOPED I, PIOPED II and another study [12,13,15]. However, these were also common in many cases for which PE was excluded. Cyanosis and fever ($> 38.5^\circ\text{C}$) were also found in only 11% and 7%, respectively, of patients with confirmed PE [13,15].

4. Asymptomatic presentation on scanning

Asymptomatic and previously unsuspected PE are increasingly being detected in a variety of patients, as a result of the wider use and greater sensitivity of scanning techniques [16]. This is notably the case in patients with chronic lung disease and in those with cancer, partly owing to greater use of computed tomography (CT) in oncological staging [17]. CT scans found asymptomatic venous thromboembolism (VTE) in 6.3% of patients with cancer, of which 3.3% of cases were PE [18]. However, this may not translate to daily practice, because these scans were subject to careful re-assessment. A retrospective analysis of 1466 consecutive staging CT scans showed asymptomatic VTE in 2.5% of patients with cancer (95% confidence interval [CI] 1.60–3.80). This included 1.3% of patients with incidental PE or thrombosis of the inferior vena cava (IVC), iliac vein or femoral veins (95% CI 0.70–2.30) and 1.1% with abdominal vein thrombosis [19].

5. Asymptomatic presentation in association with DVT

Routine screening of patients with symptomatic, proven DVT demonstrated an unexpectedly high proportion (51%) with probable asymptomatic PE detected by ventilation-perfusion scintigraphy (V/Q) scan [20]. In the international Registro Informatizado de Enfermedad TromboEmbólica (RIETE) registry, 35% of the 2375 patients with a proximal lower-limb DVT had asymptomatic PE [21].

Diagnosis of Patients with Pulmonary Embolism

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

Initial Diagnostic Stratification Based on Mortality Risk

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

Confirmatory Diagnostic Testing in High-risk Patients

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

Table 1
European Society of Cardiology risk stratification for patients with pulmonary embolism [10].

Parameter	High risk	Intermediate risk	Low risk
Presence of shock ^a or hypotension ^b	Yes	No	No
Right ventricular dysfunction ^c and myocardial injury ^d	Does not need to be determined if patient has shock or hypotension	Either or both present	No
30-day mortality rate	>15%	3–15%	<1%
Clinical management	Emergency intervention	Admit to hospital	Early discharge or care at home

^a Blood pressure <90 mm Hg.
^b Blood pressure drop of 40 mm Hg below usual level.
^c Right ventricular dilation; hypokinesis or pressure overload on echocardiography; right ventricular dilatation on spiral computed tomography; brain natriuretic peptide or N-terminal pro-brain natriuretic peptide elevation, elevated right heart pressure.
^d Positive cardiac troponin T or I.

performed in acute situations to confirm a suspected high-risk PE. If CTPA is unavailable or the patient's condition allows only bedside investigations, echocardiography may be used (Fig. 1). In unstable patients, evidence of acute pulmonary hypertension and RV overload on echocardiography can justify thrombolysis or embolectomy. RV overload on echocardiography may also be sufficient for considering treatment when other tests, such as transoesophageal echocardiography for PE or compression ultrasonography (CUS) for DVT, are unavailable [10]. Thrombosis seen on transoesophageal echocardiography and CUS may help with decision-making. An RV/left ventricular hazard ratio (HR) of >0.9, and elevated markers of RV dysfunction/dilation and myocardial injury (brain natriuretic peptide and standard troponin T or I, respectively), are of prognostic significance [10].

If PE is confirmed, the Pulmonary Embolism Severity Index (PESI) score can help to estimate the 30-day mortality risk [24–26]. A value is ascribed to each of the 11 variables present, and a total is then determined by summing the points and adding the patient's age in years. In the simplified PESI (sPESI), which takes into account only age, history of cancer, chronic cardiopulmonary disease, elevated pulse, low blood pressure and low oxygen saturation, any patient with at least one risk factor is considered at high risk of death (Table 2) [27,28].

Table 2
Simplified PESI score for assessing the likelihood of PE-related death [28].

Parameter	Score
Age >80 years	1
History of cancer	1
Chronic cardiopulmonary disease	1
Pulse ≥ 110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxyhaemoglobin saturation level <90%	1

Any patient scoring 1 point or more is considered to be at high risk of early death.
Abbreviations: PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index.

Further Stratification and Confirmatory Diagnostic Testing in Non-high-risk Patients

Patients without shock and/or hypotension are considered non-high-risk and require appropriate diagnosis, further risk stratification and treatment [10]. The presence of RV dysfunction or signs of myocardial injury suggests an intermediate (3–15%) risk of early death, whereas the absence of all these signs correlates with a low (<1%) mortality risk (Table 1) [10].

Determining Clinical Probability of Non-high-risk PE using Clinical Risk Scores

Clinical judgement or validated prediction rules (e.g. the Wells score) are beneficial in categorising a patient's pre-test probability of PE based on initial findings and predisposing risk factors for PE. Although 30% of PE cases occur without any known cause [10], patient-and setting-related factors can help to categorise patients based on clinical probabilities. Subsequent investigations and examinations to exclude PE can then be viewed in light of the clinical risk score and the results of initial investigations [10].

Other clinical risk scores have been developed based on clinical observations that correlate with a positive diagnosis. These include the Wells, Geneva and Miniati scores, and the Pulmonary Embolism Rule-Out Criteria [29–34]. The Wells score is the most extensively validated and commonly used of these [29,35–37]. Using the Wells score, the clinical probability of PE is assessed as low (<2.0), moderate (2.0–6.0)

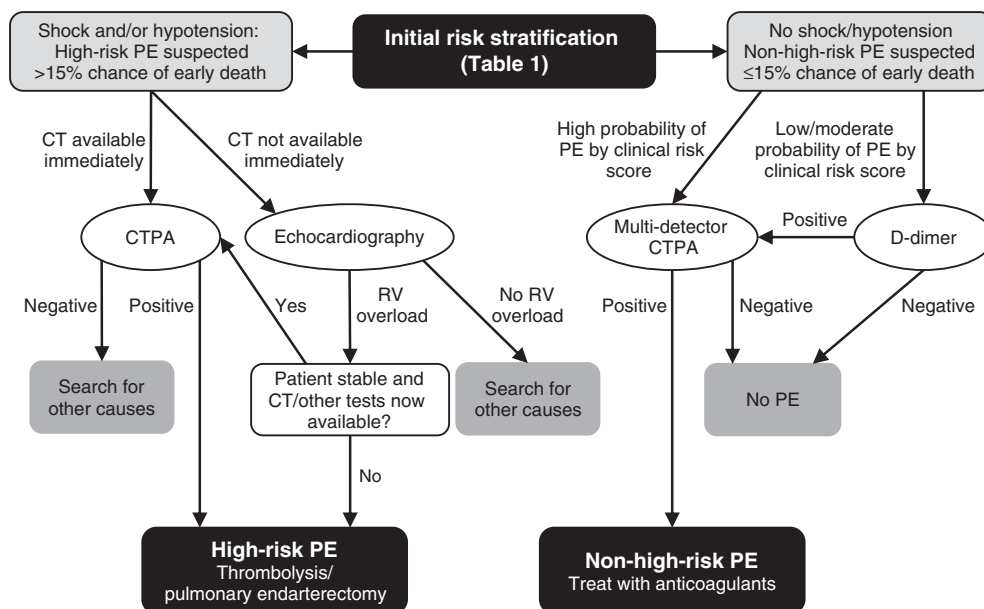


Fig. 1. Diagnostic pathway recommended by the European Society of Cardiology for risk stratification of patients with PE [10]. **Abbreviations:** CT, computed tomography; CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism; RV, right ventricular.

or high (>6.0) by adding up values given to common clinical signs and symptoms of PE and clinical judgement (Table 3) [29]. Clinical signs and symptoms of DVT (3.0) and the clinician's judgement that an alternative diagnosis is less likely than PE (3.0) carry the most weight [29]. Simplified versions of both the Wells and Geneva scores have been created and have a similar predictive value to the original scores [38].

High Clinical Probability of Non-high-risk PE

Further investigations, such as imaging, are required in these patients, and CTPA should be carried out in all patients with a moderate or high clinical probability of PE. A positive CTPA (Fig. 2) confirms a PE that should be treated, typically with low molecular weight heparin (LMWH), whereas a negative multi-detector CTPA safely excludes PE [39–42]. By contrast, single-detector CTPA cannot exclude PE [43,44]. Equivocal CTPA results should prompt further testing, possibly including chest X-ray (CXR), D-dimer testing, repeat CTPA, lower-limb Doppler scanning or a conventional pulmonary angiogram.

A V/Q scan is an alternative to CTPA if a patient has a moderate or high pre-test probability of PE, despite normal CXR and D-dimer results (for example, if CTPA is contraindicated owing to renal impairment or allergy to the contrast agent). V/Q scan results are usually divided into the five categories established by the PLOPED trial: normal, near-normal-, low-, intermediate- (non-diagnostic), and high-probability of PE [45]. A high-probability (two or more mismatched segmental perfusion defects) V/Q scan confirms PE, and the patient should be started on treatment. A normal- or high-probability V/Q scan excludes or confirms a suspected PE in most patients [45,46], and non-diagnostic, low-probability results combined with low clinical probability show a very low prevalence of PE [45,47]. The combination of clinical probability, D-dimer, CUS and lung scanning confirms or excludes PE in 94% of patients [48]. However, considered alone, intermediate-probability V/Q scan results or a low- or normal-probability scan in a patient with a high pre-test probability of PE require CTPA to rule out PE. The high frequency of these intermediate scans has led critics to question the usefulness of V/Q scanning in excluding PE [10].

Lower-limb CUS can also provide alternate rationale for therapy either in patients with a high clinical probability of PE with a suspected false-negative CTPA result or when CTPA is contraindicated [40,49]. Anticoagulant treatment can be justified when a proximal DVT is present, because this is found in 30–50% of patients with PE [50,51]. DVT can be diagnosed using CUS with a 90% sensitivity and 95% specificity for proximal DVT. In patients with suspected PE, proximal DVT warrants anticoagulation without further testing [52]. CUS can also reduce the chance of a false-negative result with single-detector CTPA.

Pulmonary angiography was formerly the 'gold standard' for PE diagnosis. Non-invasive diagnostic investigations such as CTPA, D-dimer assays, lower-limb CUS and V/Q exams have largely removed the need for this more invasive and costly technique [10,53,54], which is now mostly used only when other test results are unclear [10].

Table 3

Wells score^a for prediction of PE [29].

Parameter	Score
Clinically suspected DVT	3
Alternative diagnosis less likely than PE	3
Rapid heart rate	1.5
Immobilisation within past 4 weeks	1.5
History of DVT	1.5
Haemoptysis	1
Malignancy	1

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

^a A total score >6 indicates a high probability of a PE, 2–6 moderate probability and <2 low probability.



Fig. 2. Computed tomography pulmonary angiography scan of a bilateral pulmonary embolism.

Low-to-moderate Clinical Probability of Non-high-risk PE

Quantitative enzyme-linked immunosorbent assay (ELISA) D-dimer assays and other ELISA-derived tests have a high sensitivity (>95%) and a specificity of approximately 40% [10]. Patients with a normal high-specificity D-dimer assay result and a low pre-test probability can safely be excluded from having PE. Only low pre-test probability patients can be excluded with a moderately sensitive assay. Assay specificity decreases with age, active malignancy and pregnancy [10]. D-dimer is also often elevated in hospitalised patients and is, therefore, of limited use in this setting. Recently, it was found that doubling the concentration threshold that conventionally denotes a positive D-dimer result (from <500 to <1000 ng/ml) in elderly (age >70 years) or low-clinical-risk patients reduced the need for subsequent CTPA without a significantly increased risk of missing PE or pneumonia [55].

Other common laboratory tests and investigations may exclude other causes for PE-like signs and symptoms but lack sensitivity or specificity for PE. A CXR may help to exclude other causes for dyspnoea and chest pain [10]. However, the most frequently observed abnormalities in CXRs are also non-specific [56]. Levels of arterial blood gases can remain normal in up to 21% of patients with PE who have no history of prior cardiopulmonary disease [57], and may be abnormal in patients both with and without PE [58]. Recent changes in electrocardiography indicative of RV strain (inversion of T waves in leads V1–V4, a QR pattern in lead V1, S1Q3T3 type incomplete or complete right bundle-branch block) may be helpful, but these changes are also found in RV strain of any cause [10,59]. A normal CXR and D-dimer assay with a low pre-test probability rules out PE. PE can also be excluded in patients with an abnormal CXR, normal D-dimer assay and low pre-test probability.

Although at least 25% of patients with PE show RV dilation on an echocardiogram or CTPA [10], the low sensitivity (60–70%) of the test in non-high-risk patients means an echocardiogram cannot exclude PE [47,60–64]. However, echocardiography can help to risk-stratify non-critical patients and the absence of signs of RV overload on an echocardiogram can exclude PE as a reason for haemodynamic instability.

Treatment of Primary Pulmonary Embolism

High-risk PE

High-risk PE is severe and life-threatening, and restoration of pulmonary arterial flow is a priority to prevent RV failure. In such cases, immediate anticoagulation with intravenous unfractionated heparin (UFH) and thrombolytic therapy are recommended, with

surgical intervention as a back-up in case of a contraindication to, or failure of, thrombolysis [10,65]. In the latter case, both sets of guidelines recommend surgical or catheter embolectomy. Streptokinase, urokinase or recombinant tissue plasminogen activator (rtPA) are the recommended thrombolytic drugs [10,65] and should preferably be given over a short 2-hour infusion period, which is associated with more rapid clot lysis and a reduced risk of bleeding than prolonged infusion [65]. For this reason, rtPA, which can be infused over a short duration, is commonly used. Thrombolysis significantly reduces the incidence of recurrent PE and death compared with heparin [10,65,66], and was effective in 92% of patients in one study [67].

Non-high-risk PE

Thrombolysis

Four recent randomised trials have investigated thrombolysis in intermediate-risk PE. The first of these to be published was the MOderate Pulmonary Embolism Treated with Thrombolysis (MOPETT) study, in which 121 patients with intermediate-risk PE were randomised to a moderate dose of rtPA plus anticoagulation or anticoagulation alone over 22 months [68]. Thrombolysis led to a significant reduction in pulmonary hypertension and recurrent PE at 28 months (16% vs. 57%; $P < 0.001$), duration of hospitalisation (2.2 days vs. 4.9 days; $P < 0.001$) and death or recurrent PE (1.6% vs. 10%; $P = 0.0489$), with no bleeding in either group. At the 2013 annual meeting of the American College of Cardiology (ACC), several further studies were presented. A small, randomised study (ULtrasound Accelerated Thrombolysis of Pulmonary Embolism [ULTIMA]; $n = 57$) of endovascular catheter-directed rtPA 10 mg infused over 15 hours with UFH, or UFH alone, in patients with intermediate-risk PE found a significant 23% improvement in right heart function among patients given endovascular thrombolysis, as measured by the RV/left ventricular ratio, compared with anticoagulation alone (3% improvement; $P < 0.0001$) [69,70]. This improvement continued to be statistically significant at 90 days ($P < 0.0001$). Another small,

randomised study (Tenecteplase or Placebo: Cardiopulmonary Outcomes At Three Months [TOPCOAT]; $n = 83$) found that thrombolysis with tenecteplase plus LMWH was superior to LMWH alone in terms of 5-day survival to hospital discharge without shock, intubation or major haemorrhage in patients with intermediate-risk PE (65% vs. 40%; $P = 0.02$), while fewer additional patients treated with tenecteplase/LMWH compared with LMWH alone had non-favourable outcomes at 3 months (13 vs. 23) [71].

A much larger study, the Pulmonary Embolism Thrombolysis trial (PEITHO), was also presented at ACC 2013. In this trial, 1006 patients aged ≥ 18 years with intermediate-risk PE were randomised to receive thrombolysis with weight-adjusted intravenous tenecteplase or placebo, both with standard heparin anticoagulation [72]. Thrombolysis reduced the risk of mortality from any cause and haemodynamic collapse within 7 days of randomisation (2.6% vs. 5.6%; $P = 0.015$), mainly as a result of a significant reduction in haemodynamic collapse ($P = 0.002$), but at a cost of a significant increase in non-intracranial major bleeding (6.3% vs. 1.5%; $P < 0.001$) and stroke (2.4% vs. 0.2%; $P = 0.003$) [73].

Anticoagulation

The current guidelines recommend anticoagulation rather than thrombolysis for non-high-risk presentations of PE [10,65]. The ACCP recommendations for the treatment of PE categorise anticoagulation into three phases: initial (up to approximately 7 days); long-term (approximately 7 days to approximately 3 months) and extended (approximately 3 months to indefinite) [65]. Recommendations issued by the ESC [10] describe initial and long-term anticoagulation for PE. Although the terminology used by these guidelines differs, they broadly concur on most key points (Table 4) [10,65]. Notably, the more recent ACCP guidelines now provide preliminary advice on the non-VKA OACs, which were not available when the ESC issued its guidance.

For initial anticoagulation, LMWH or fondaparinux are preferred over UFH (unless, according to the ESC, the patient has a high risk of bleeding or has severe renal dysfunction) [10,65]. Parenteral anticoagulation

Table 4

Summary and comparison of recommendations for the treatment of PE; ESC 2008 and ACCP 2012 [10,65]. Notable differences are highlighted in bold.

Setting	ESC 2008	ACCP 2012
Acute PE (ACCP)/low-to-intermediate risk PE (ESC)	Initial treatment with UFH, LMWH or fondaparinux initiated while the diagnostic work-up is still ongoing (LMWH/fondaparinux preferred over UFH except in patients with high bleeding risk or severe renal impairment) for: <ul style="list-style-type: none"> • 5 days followed by transition to VKA once INR has remained in the target range for at least 2 consecutive days, continuing for: <ul style="list-style-type: none"> – 3 months if PE is secondary to a transient risk factor – 3 or more months for a first or subsequent unprovoked PE with a low bleeding risk VKA dose should be adjusted to maintain an INR of 2.5 (range 2.0–3.0)	Initial treatment with parenteral anticoagulant (LMWH/fondaparinux preferred over UFH) or rivaroxaban for: <ul style="list-style-type: none"> • 5 days followed by transition to VKA once INR has remained in the target range of 2.0–3.0 (target 2.5) for at least 24 hours, continuing for: <ul style="list-style-type: none"> – 3 months if provoked by surgery or a non-surgical risk factor, or if bleeding risk is high – More than 3 months for a first or subsequent unprovoked PE with low/moderate bleeding risk VKA dose should be adjusted to maintain an INR of 2.5 (range 2.0–3.0)
PE associated with hypotension (ACCP and ESC) and/or shock; other high-risk PE (ESC)	<ul style="list-style-type: none"> • Anticoagulation with UFH initiated immediately • Thrombolytic therapy, haemodynamic and respiratory support • If thrombolysis is absolutely contraindicated or has failed, options are: <ul style="list-style-type: none"> – Surgical embolectomy (preferred) – Catheter embolectomy • Fragmentation of proximal pulmonary arterial clots with catheters where appropriate 	<ul style="list-style-type: none"> • Initial anticoagulation with i.v. UFH rather than s.c. therapies • Thrombolytic therapy • If thrombolysis is absolutely contraindicated or has failed, options are: <ul style="list-style-type: none"> – Catheter embolectomy (preferred) – Pulmonary embolectomy
PE associated with active cancer	Initial treatment with LMWH for 3–6 months, after which LMWH or VKA should be continued indefinitely or until the cancer is cured	Initial treatment with LMWH preferred over VKA, continuing for more than 3 months
PE in pregnancy	After confirmatory diagnosis, anticoagulation is recommended (LMWH is preferred; VKAs may be used with caution in the second trimester only) and should be continued for at least 3 months after delivery	LMWH is preferred to UFH and should continue for at least 6 weeks post-partum (minimum duration of therapy of 3 months)
Patients with CTPH	Pulmonary endarterectomy	Extended anticoagulation: pulmonary thromboendarterectomy if appropriate expertise is available
PE in patients with severe renal insufficiency (CrCl <30 ml/min)	UFH preferred to LMWH owing to lack of renal clearance	UFH preferred to LMWH, rivaroxaban and dabigatran owing to lack of renal clearance
PE in children	No specific recommendations provided	Initial UFH/LMWH, with LMWH or VKA preferred long term

Abbreviations: ACCP, American College of Chest Physicians; CrCl, creatinine clearance; CTPH, chronic thromboembolic pulmonary hypertension; ESC, European Society of Cardiology; INR, international normalised ratio; i.v., intravenous; LMWH, low molecular weight heparin; PE, pulmonary embolism; s.c., subcutaneous; UFH, unfractionated heparin; VKA, vitamin K antagonist.

should be started in cases of strongly suspected PE, even if diagnostic work-up has not been completed [10,65]. VKA therapy should also be initiated as soon as possible and parenteral anticoagulation discontinued after 5 days or when the international normalised ratio (INR) stabilises within the target range of 2.0–3.0 (target 2.5) for at least 24 hours (ACCP) [65] or 2 consecutive days (ESC) [10]. The ACCP guidelines have a weak recommendation for traditional parenteral agents over oral rivaroxaban (Xarelto®, Bayer HealthCare AG, Berlin, Germany) or dabigatran (Pradaxa®, Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany) but they do acknowledge that emerging data with non-VKA OACs means that this is likely to change [65]. Indeed, regulatory authorities have given approval for rivaroxaban for the treatment of DVT and PE and prevention of recurrence [74,75].

Guidelines also discuss the use of IVC filters in patients with PE and recommend insertion of an IVC filter only when anticoagulation is contraindicated, and the ESC adds ‘when the risk of recurrent VTE is high’ [10,65]. There are no data on the use of non-VKA OACs with thrombolytic therapy. In theory, it might be possible after lysis to treat with UFH/LMWH for 2 days and then consider switching to a non-VKA OAC rather than starting a VKA.

Of the phase III clinical trials of non-VKA OACs for the treatment of PE, the EINSTEIN PE trial of rivaroxaban is the only published study evaluating a single-agent approach specifically for the treatment of symptomatic PE [76]. In this multicentre, randomised, open-label, non-inferiority study, 4832 patients with confirmed acute symptomatic PE with or without symptomatic DVT were recruited, but the most severely ill patients were excluded, as per the guidelines [76]. A single pre-study dose of parenteral anticoagulant was permitted and received by 92% of patients. Patients were treated for 3, 6 or 12 months (based on a clinical evaluation of individual risk for recurrent thrombosis and bleeding) with either rivaroxaban 15 mg twice daily (bid) for the first 3 weeks followed by 20 mg once daily (od) thereafter, or the standard approach of enoxaparin 1 mg/kg bid transitioning to a VKA started no later than 48 hours after randomisation [76]. VKA doses were adjusted to maintain a target INR of 2.0–3.0 [76].

Rivaroxaban was non-inferior to enoxaparin/VKA for the primary efficacy endpoint of recurrent symptomatic VTE (fatal plus non-fatal PE and/or DVT; $P = 0.003$ for non-inferiority; Table 5) [76]. Interestingly, rates of recurrent VTE were similar regardless of the anatomical extent of initial PE (1.6% vs. 1.3% for limited lung involvement, 2.5% vs. 2.2% for intermediate involvement and 1.7% vs. 1.4% for extensive involvement for rivaroxaban and enoxaparin/VKA, respectively). The principal safety outcome of major plus non-major clinically relevant bleeding occurred with a similar incidence in both study arms (Table 5), but major bleeding occurred significantly less frequently among patients treated with rivaroxaban ($P = 0.003$; Table 5) [76]. These outcomes reflected those of the parallel EINSTEIN DVT trial, which included patients with DVT but not PE [77].

Other non-VKA OACs have been assessed in randomised, phase III trials for the treatment of acute PE with or without DVT. Although there were no specifically PE-focused studies among these, several included substantial numbers of patients with PE. Like rivaroxaban, apixaban (Eliquis®, Bristol-Myers Squibb Inc., New York, NY, USA) was evaluated as a single-drug treatment against standard therapy, but in a mixed population of patients with acute VTE, in the recently published randomised, double-blind phase III, AMPLIFY study [78]. In the apixaban arm, 87% of patients received a parenteral agent at the start of treatment. Approximately one-third of patients ($n = 1836$) had PE with or without DVT and a high proportion had unprovoked VTE. Apixaban (10 mg bid for 7 days, then 5 mg bid for a fixed duration of 6 months) was non-inferior to standard enoxaparin/warfarin for the incidence of recurrent VTE or VTE-related death ($P < 0.001$ for non-inferiority; Table 5) and was associated with a significant reduction in the incidence of major bleeding and major plus non-major clinically relevant bleeding ($P < 0.001$ for both; Table 5) [78].

Table 5

Overview of study design and principal efficacy and safety results from phase III studies of non-VKA oral anticoagulants for the treatment of acute PE (rivaroxaban) and acute VTE (apixaban, dabigatran and edoxaban) [76–80].

Study name	Design	Patient diagnosis	Study arms	Treatment duration	Primary efficacy outcome	Bleeding outcomes
EINSTEIN PE	Multicentre, randomised, open-label, non-inferiority	Acute symptomatic PE with or without DVT ($n = 4832$)	Single-drug rivaroxaban vs. standard therapy	3, 6 or 12 months (investigator discretion)	Recurrent symptomatic VTE: 2.1% vs. 1.8% (HR = 1.12; 95% CI 0.75–1.68; $P = 0.003$ for non-inferiority)	First major or non-major clinically relevant bleeding: 10.3% vs. 11.4% (HR = 0.90; 95% CI 0.76–1.07; $P = 0.23$) Major bleeding: 1.1% vs. 2.2% (HR = 0.49; 95% CI 0.31–0.79; $P = 0.003$) Major bleeding: 0.6% vs. 1.8% (RR = 0.31; 95% CI 0.17–0.55; $P < 0.001$) First major or non-major clinically relevant bleeding: 4.3% vs. 9.7% (RR = 0.44; 95% CI 0.36–0.55; $P < 0.001$)
AMPLIFY	Multicentre, randomised, double-blind, non-inferiority	Acute, symptomatic proximal DVT and/or PE ($n = 5400$)	Single-drug apixaban vs. standard therapy	6 months (fixed)	Recurrent VTE or related death (first episode): 2.3% vs. 2.7% (HR = 0.84; 95% CI 0.60–1.18; $P < 0.001$ for non-inferiority)	Major bleeding: 1.6% vs. 1.9% (HR = 0.82; 95% CI 0.45–1.48) Major or non-major clinically relevant bleeding: 5.6% vs. 8.8% (HR = 0.63; 95% CI 0.47–0.84)
RE-COVER	Multicentre, randomised, double-blind, non-inferiority	Acute, symptomatic proximal DVT and/or PE ($n = 2564$)	Parenteral anticoagulant/dabigatran vs. standard therapy	6 months (fixed)	Recurrent VTE or related death: 2.4% vs. 2.1% (HR = 1.10; 95% CI 0.65–1.84; $P < 0.001$ for non-inferiority)	Major bleeding: 1.6% vs. 1.9% (HR = 0.82; 95% CI 0.45–1.48) Major or non-major clinically relevant bleeding: 5.6% vs. 8.8% (HR = 0.63; 95% CI 0.47–0.84)
Hokusai-VTE	Multicentre, randomised, double-blind, non-inferiority	Acute, symptomatic DVT and/or PE ($n = 8292$)	Parenteral anticoagulant/edoxaban vs. standard therapy	3–12 months (investigator discretion)	Recurrent VTE or related death 12 months after treatment start: 3.2% vs. 3.5% (HR = 0.89; 95% CI 0.70–1.13; $P < 0.001$ for non-inferiority)	First major or non-major clinically relevant bleeding: 8.5% vs. 10.3% (HR = 0.81; 95% CI 0.71–0.94; $P = 0.004$) Major bleeding: 1.4% vs. 1.6% (HR = 0.84; 95% CI 0.59–1.21; $P = 0.35$)

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.

Two phase III, randomised, double-blind, non-inferiority trials of non-VKA OACs given after standard parenteral induction have also been published. In RE-COVER, the efficacy and safety of dabigatran etexilate (150 mg bid) versus warfarin (target INR range 2.0–3.0) was evaluated for the treatment of patients with acute, symptomatic VTE [79]. Approximately one-third of patients in this study had PE ($n = 786$). Unlike in EINSTEIN PE and AMPLIFY, all patients, not just those in the standard therapy arm, received induction with an approved parenteral anticoagulant for 5–11 days, and the total treatment duration was 6 months. The parenteral agent/dabigatran arm was non-inferior to the parenteral agent/warfarin arm for the primary efficacy endpoint, recurrent VTE or VTE-related death during the study period ($P < 0.001$ for non-inferiority; Table 5) [79]. Symptomatic, non-fatal PE, which was a secondary endpoint in RE-COVER, also occurred with a similar incidence (1.0% vs. 0.6%; HR = 1.85 [95% CI 0.74–4.64]) [79]. Rates of major bleeding, the principal safety outcome, were similar between the treatment arms (Table 5) [79]. The findings were consistent for patients with DVT and those with PE in this study.

Edoxaban (Lixiana[®], Daiichi Sankyo Co. Ltd, Tokyo, Japan) was also assessed for the treatment of VTE in the randomised, double-blind, phase III Hokusai-VTE study [80]. This study included a higher number of patients with PE than the other mixed VTE studies ($n = 3319$) [78,79], and a high proportion of these (approximately 46%) had anatomically extensive disease. As with dabigatran, patients in both study arms received a parenteral anticoagulant (LMWH or UFH) for a minimum of 5 days, followed by edoxaban 60 mg od (30 mg od in patients with creatinine clearance [CrCl] 30–50 ml/min, body weight ≤ 60 kg or receiving potent P-glycoprotein inhibitors) or overlapping transition to warfarin (INR 2.0–3.0) for up to 12 months, at the discretion of the treating physician. Unlike other studies, the primary efficacy endpoint (recurrent VTE or VTE-related death) was assessed 12 months after treatment initiation regardless of the time on treatment. Heparin/edoxaban was found to be non-inferior to heparin/warfarin according to this analysis and also during the treatment period ($P < 0.001$ for non-inferiority; Table 5) [80]. Efficacy was similar to the overall population in the subgroups of PE and DVT patients. There was a significantly lower incidence of a first major plus non-major clinically relevant bleeding event in the heparin/edoxaban arm ($P = 0.004$), but the incidence of major bleeding was not significantly different to standard therapy (Table 5) [80].

Prevention of Recurrence and Long-term Complications

After an initial PE, patients are at high risk of recurrence without continued anticoagulation [81,82]. Recurrence seems more frequent after unprovoked PE, and is more common in patients with persistent risk factors (such as active cancer and elevated antiphospholipid antibodies and/or D-dimer concentrations) and CTPH than in those for whom factors contributing to the initial event may no longer be present (e.g. surgery) [4,65]. Although one meta-analysis suggested a 3.1-fold greater risk of recurrent VTE with initial symptomatic PE than for initial proximal DVT [83], this finding has not been consistently demonstrated in all studies [84]. Indeed, in EINSTEIN DVT and EINSTEIN PE, the rate of VTE recurrence was 2.5% after initial DVT (with just over half of recurrences being PE) [77] compared with 1.9% after initial PE (with a new PE approximately 1.5 times more common than a new DVT) [76]. Mortality as a result of recurrent VTE is higher in patients with PE than in those with DVT [82] and may be increased in patients with CTPH [65].

Duration of Anticoagulation

For the above reasons, patients who receive successful treatment for initial PE with acute and prolonged therapy require close follow-up after discharge from hospital and, in many cases, will require extended

anticoagulation (longer than 3 months). The period of anticoagulation recommended by the guidelines varies according to a patient's risk status (Table 4). If the risk of bleeding is high and/or factors potentially contributing to the initial PE are no longer present, 3 months' treatment is proposed [10,65]. Conversely, if the risk of bleeding is lower and/or risk factors remain, or the PE was apparently unprovoked, anticoagulation beyond 3 months is encouraged [10,65]. Patients with CTPH are recommended to undergo pulmonary endarterectomy. However, in the absence of suitable expertise or if the lesion is not surgically remediable (e.g. a distal obstruction), the ACCP guidelines recommend extended anticoagulant therapy [10,65].

To investigate long-term rivaroxaban for secondary VTE prevention, an extension study was conducted. In EINSTEIN EXT, rivaroxaban (20 mg od) or placebo was given for 6 or 12 months to patients who had completed 6–12 months of VKA or rivaroxaban treatment for initial symptomatic DVT or PE [77]. Approximately 19% of patients from EINSTEIN PE entered EINSTEIN EXT. In the overall population, rivaroxaban was superior to placebo for the incidence of recurrent DVT, non-fatal PE, fatal PE or unexplained death possibly related to PE (1.3% vs. 7.1%; HR = 0.18 [95% CI 0.09–0.39]; $P < 0.001$ for superiority), with major bleeding seen in only 4/602 (0.7%) patients receiving rivaroxaban and none of the 594 placebo recipients; there were no fatal bleeding events and no major bleeding events at a critical site [77]. In the RE-MEDY trial, extended dabigatran treatment was non-inferior to warfarin for the prevention of recurrent VTE and VTE-related death when given after successful anticoagulant treatment of initial VTE (1.8% vs. 1.3%; HR = 1.44 [95% CI 0.78–2.64]; $P = 0.03$ for non-inferiority) [85]. In addition, in the RE-SONATE study, dabigatran was superior to placebo for long-term prevention of recurrent symptomatic VTE in patients who had received 6–18 months of VKA treatment for initial symptomatic DVT or PE (0.4% vs. 5.6%; HR = 0.08 [95% CI 0.02–0.25]; $P < 0.0001$ for superiority) [86]. However, in RE-MEDY, although rates of major bleeding were similar (0.9% vs. 1.8%; HR = 0.52 [95% CI 0.27–1.01]), acute coronary syndrome events occurred with a significantly higher incidence in the dabigatran arm (0.9% vs. 0.2%, respectively; $P = 0.02$) [85]. In RE-SONATE, major bleeding occurred in two patients (0.4%) receiving dabigatran and none in the placebo group ($P = 0.5$), and, as expected for a placebo comparison, clinically relevant bleeding occurred significantly more frequently with active treatment ($P = 0.001$) [86]. In the AMPLIFY-EXT study of apixaban (2.5 or 5 mg bid) versus placebo given for 12 months in patients who had completed 6–12 months of anticoagulation treatment, there was a significant reduction in recurrent VTE or VTE-related death with apixaban compared with placebo (1.7% for both apixaban doses vs. 8.8%; $P < 0.001$) with minimal ($\leq 0.5\%$) major bleeding in both the treatment and placebo arms [87].

Recently, there has been renewed interest in the potential benefits of acetylsalicylic acid (ASA) in thromboembolic disorders. In the multicentre, randomised, double-blind WARFASA study, patients who had experienced an initial VTE and completed 6–18 months of OAC therapy were randomly assigned to ASA 100 mg od or placebo for a further 2 years, with the option of extension [88]. The incidence of VTE recurrence was lower in patients receiving ASA (28/205 vs. 43/197 with placebo; 6.6% vs. 11.2% per year; HR = 0.58 [95% CI 0.36–0.93]). Only one patient in each arm had a major bleeding event, and adverse event profiles were similar. The positive effect of ASA remained regardless of whether the initial event was PE or DVT, and irrespective of age, sex and duration of initial anticoagulation [88]. Another similar study, ASPIRE, failed to demonstrate statistical superiority for ASA over placebo for prevention of recurrent VTE in patients who had previously been treated for VTE with anticoagulants (rates of 4.8% vs. 6.5% per year; $P = 0.09$), but ASA did show a cardioprotective effect, reducing the rate of VTE, myocardial infarction, stroke or cardiovascular death by 34% ($P = 0.01$), without an increase in major bleeding compared with placebo (1.1% vs. 0.6% per year; $P = 0.22$) [89].

Special Patient Groups

As mentioned previously, guidelines recommend extended anticoagulation while the benefit–risk balance remains favourable (Table 4), and this needs to be considered in patients at high risk of bleeding. This also applies to patients with active cancer, in whom studies have shown a preference for long-term LMWH rather than short-term LMWH followed by VKA. Non-VKA OACs are not recommended for pregnant women, who should receive LMWH [10,65]. Patients with severe renal impairment (CrCl <30 ml/min), who are at increased risk of bleeding, are recommended to receive UFH and to be carefully assessed after the initial 3-month treatment window for the benefit of continued therapy [10,65]. Minimal data exist regarding anticoagulation in paediatric patients, but the ACCP recommends initial UFH or LMWH, with LMWH or VKA preferred in the long term [90].

Discussion

The risk of early death from PE necessitates rapid treatment decisions. Although clinical diagnosis is difficult, increasingly sophisticated scanning techniques and risk scores allow stratification of patients by early mortality risk. However, some of these tests take time, and guidelines recommend initiation of parenteral anticoagulation when PE is clinically suspected, regardless of whether or not a definite diagnosis has been established [10,65].

Thrombolysis accompanied by UFH is the established treatment approach to high-risk PE and has been shown to be effective in these patients who require urgent clot lysis [10,65,66]. For intermediate-risk PE, the picture is less clear. Data from small studies suggest a possible role for thrombolysis at a reduced dose [68–71]. However, the results of the much larger, randomised PEITHO study of tenecteplase plus anticoagulation versus anticoagulation alone in intermediate-risk patients with PE indicated an excess of major bleeding and stroke with thrombolysis [73], suggesting that a benefit is by no means clear-cut. It should also be noted that tenecteplase is not currently recommended for thrombolysis, and that current guidelines do not support thrombolysis in non-high-risk patients [10,65].

For PE classified as non-high risk, the traditional approach to anticoagulant treatment – a parenteral agent overlapping with and transitioning to an oral VKA – is based on the need for a rapid anticoagulant effect (an advantage of subcutaneous or intravenous formulations) balanced with the practical advantages of oral treatment during the secondary prevention phase. However, the transition requires close monitoring of the INR, which must then also be tightly controlled for the entire period of VKA therapy. In practical terms, this is difficult. Two large cohort studies using healthcare insurance databases indicated that patients treated for VTE with warfarin remained in the therapeutic range only 38% of the time [91,92]. Non-VKA OACs offer a potential alternative by providing a fast-acting anticoagulant effect with fixed oral dosing and without the need for routine coagulation monitoring. Rivaroxaban and apixaban alone, and dabigatran and edoxaban after parenteral anticoagulant induction, were non-inferior to standard therapy for the prevention of recurrent VTE [76–80]. The risk of major bleeding was similar after parenteral induction with dabigatran and edoxaban and significantly reduced with single-drug rivaroxaban or apixaban [76–80].

After an initial PE, patients should continue to receive anticoagulants to prevent recurrence [10,65]. Treatment usually continues for at least 3 months and often longer, or even indefinitely, provided that the risk of bleeding continues to be outweighed by the potential therapeutic benefits (Table 4). Although initial management may occur in the inpatient or outpatient setting, depending on the severity of PE (Table 1) and local practice, most patients will self-administer anticoagulant treatment at home at some point, supported by general practitioner or nurse visits, or sessions at an anticoagulation clinic or pharmacy. In this context, patients may prefer oral agents over parenteral

drugs that require injection by the patient, a family member, carer, nurse or doctor, with potential consequences for adherence. Meta-analysis data involving approximately 6500 patients have indicated that patients can safely self-manage their anticoagulation with no detrimental effect on efficacy and safety [93], and several countries have adopted or are considering this approach. Nevertheless, unlike VKAs, non-VKA OACs are given at fixed doses without the need for routine monitoring and could, therefore, further ease the burden on both patients and healthcare practitioners.

Guidelines tend to view any therapy after 3–6 months as extended treatment; studies such as EINSTEIN EXT [77], RE-MEDY [85] and AMPLIFY-EXT [87] have shown a continued benefit with anticoagulation for between 12 months and 3 years, albeit with a small increase in the risk of bleeding and possibly, in the case of dabigatran, acute coronary syndrome events [77,85]. ASA also appears to have a benefit in this scenario [88,89], although it should be noted that the reduction in recurrent VTE was much greater in the studies of non-VKA OACs, without a large difference in rates of major bleeding. Guidelines provide recommendations for balancing benefits and risks but, ultimately, the clinician will decide the type and length of treatment on a case-by-case basis.

As scanning techniques become more sensitive, asymptomatic PE is increasingly being detected [16]. Most of these emboli are small and located in segmental and subsegmental vessels [16]. Detected in isolation and without clinical symptoms, these emboli probably do not require anticoagulant treatment because evidence suggests that patients are not at an increased risk of adverse outcomes or death [94,95]. However, anticoagulation would be mandated if the patient's cardiopulmonary function is compromised or a concomitant proximal DVT is present [95].

Non-VKA OACs have predictable pharmacokinetic and pharmacodynamic characteristics that make them effective, safe and convenient for a wide range of patients. In particular, and in contrast to VKAs, demographic characteristics such as sex and ethnicity, advanced age, mild or moderate renal impairment, and low and high body weight do not necessitate dose adjustments [96]. However, there are circumstances in which non-VKA OACs may not be appropriate for treating PE and preventing recurrence, such as in critically ill patients who require surgery or thrombolysis; during pregnancy; in children; and in patients with severe renal impairment (CrCl <30 ml/min). The EINSTEIN studies, for example, recruited relatively few patients with renal impairment, and those with a clinically relevant bleeding risk were excluded [76,77]; therefore, there is limited information about the use of rivaroxaban in these patients, and caution should be applied. There is currently no specific reversal agent for rivaroxaban or any non-VKA OAC although, given their short half-lives, standard management strategies may be sufficient to control mild or moderate bleeding. Use of prothrombin complex concentrates, active prothrombin complex concentrates or recombinant Factor VIIa may be considered to attempt to reverse the action of these agents in an emergency [97,98].

In conclusion, the treatment of PE requires both a short-term and a long-term view. Clinical risk scores and diagnostic tests provide a means to stratify patients by risk of early death and to treat them accordingly. Patients may need to continue anticoagulation for several months or even years. Although traditional agents are effective, the non-VKA OACs are likely to confer practical advantages in terms of regular, fixed, oral dosing that will benefit both patients and healthcare practitioners.

Conflict of Interest Statement

ATC has received consultancy fees and clinical trial funding from pharmaceutical companies, including Bayer, Boehringer-Ingelheim, BMS, Daiichi, GSK, Johnson and Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi-Aventis, Schering Plough and Takeda. MD and MMPP

have no conflicts of interest to declare. All authors confirm that they had full access to data and contributed to the drafting of the paper.

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