Acute pulmonary embolism: risk assessment, risk stratification and treatment options

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Abstract

Introduction: Pulmonary embolism (PE) is a potentially life-threatening cardiovascular emergency with a high mortality rate. Rapid diagnosis and treatment are important in optimising clinical outcomes in patients with PE, and anticoagulants are the mainstay of treatment. Traditionally, anticoagulant therapy involves parenteral anticoagulants, overlapping with and followed by oral vitamin K antagonists. Direct oral anticoagulants (DOACs), including the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, and the direct thrombin inhibitor dabigatran etexilate, have been developed to address limitations associated with traditional anticoagulant therapy. Apixaban, dabigatran and rivaroxaban have recently been approved for the treatment of acute deep vein thrombosis (DVT) and PE and prevention of recurrent DVT or PE. Edoxaban is approved in the United States but not currently in the European Union for the treatment of DVT and PE; approval of edoxaban in Europe is anticipated in the near future.

Objective: To summarise the management of patients with suspected PE in accordance with recent guidelines, and to discuss the evidence behind the recent approvals of the DOACs for the treatment of PE.

Discussion: Diagnosis and treatment of PE is guided by clinical probability scoring systems and tools for prognostic stratification and early mortality risk evaluation. Anticoagulants remain the mainstay of treatment. Successful phase III trials have demonstrated the efficacy of the DOACs for the treatment of DVT and PE, with a potentially improved safety profile, leading to their recent approval in this indication, and giving the clinician greater choice of anticoagulant therapies in this setting.

Conclusions: DOACs offer an alternative and potentially simplified option for anticoagulation therapy in patients with PE compared with traditional anticoagulants and are likely to assist physicians in optimising management of patients with PE and improve clinical outcomes.

Key words

anticoagulants – clinical trials, phase III – diagnosis – risk assessment – pulmonary embolism – prognosis

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Both authors contributed equally to the conception of the article, the literature research, and to discuss the evidence behind the recent approvals of the DOACs for the treatment of PE.

Ethics

This review article is based on published studies, for which appropriate ethics committee approvals were obtained, and no new additional studies in patients were undertaken.

Conflicts of interest

Franco Piovella served as principal investigator, Steering Committee member or national coordinator in studies on direct oral anticoagulants sponsored by Sanofi-Aventis, Boehringer Ingelheim, Bayer, Pfizer/Bristol-Myers Squibb and Daiichi Sankyo, and received honoraria to be in speaker bureau or on scientific advisory boards of GlaxoSmithKline, Bayer, Sanofi-Aventis, Boehringer Ingelheim and Daiichi Sankyo. Diana Irina Iosub has no conflicts of interest to declare.
Introduction

Pulmonary embolism (PE) is a potentially life-threatening cardiovascular emergency that occurs when a blood clot completely or partially blocks an artery in the lung. Epidemiological studies in different countries, including the United States, China, Korea and Germany, showed that the annual incidence of acute PE in hospitalised patients ranges from approximately 0.1% to 0.4% (1–4). The mortality rate associated with PE is high. Approximately 10% of symptomatic PE cases are fatal within 1 h of first symptoms (5). The case–fatality rate without treatment was reported as approximately 15% in patients who were haemodynamically stable, rising to 58% in patients who were haemodynamically unstable (6).

The fundamentals for achieving an optimal clinical outcome for patients with PE rely upon probability assessment, rapid diagnosis, risk stratification and anticoagulation treatment. In recent years, the concepts of mortality risk evaluation and prognostic stratification in patients with PE have been developed to inform and assist the selection of appropriate initial therapy and to enable planning of long-term patient management. Anticoagulation has been shown to reduce the mortality rate to approximately 2% in haemodynamically stable patients and to approximately 13% in haemodynamically unstable patients who may also initially receive other treatment interventions such as thrombolysis or embolectomy (7). In recent years, direct oral anticoagulants (DOACs) – including the factor Xa inhibitors rivaroxaban, apixaban and edoxaban, and the thrombin inhibitor dabigatran etexilate – have been developed to address the limitations of standard of care. These DOACs have successfully completed phase III trials for the treatment of acute venous thromboembolism (VTE). To date, rivaroxaban and apixaban (as single-drug therapies) and dabigatran (after 5–10 days parenteral therapy) have been approved in the United States and Europe for the treatment of acute deep vein thrombosis (DVT) or PE and the prevention of recurrent DVT or PE. In addition, edoxaban is approved (after 5–10 days parenteral therapy) in the United States, but not currently in the European Union for the treatment of DVT and PE; approval of edoxaban in Europe is anticipated in the near future. Current guidelines reflect recent developments and recommend traditional therapy with parenteral anticoagulants and vitamin K antagonists (VKAs) or suggest therapy with DOACs as an alternative option (8, 9).

Because DOACs offer an alternative and potentially simplified treatment option with patient outcomes that are at least as good as traditional therapy, it is time to look at the evidence, to challenge current habits and to implement change where appropriate.

This review summarises and compares current risk stratification and prognostic tools for patients with suspected or confirmed PE, as well as guidelines for the diagnosis and management of PE. We also review the clinical data from recent trials of the DOACs and discuss the potential of these agents in the treatment of PE.

Initial clinical assessment – probability scores

Clinical signs and symptoms of PE can vary greatly between individuals. The most common symptoms among patients presenting with acute PE are shortness of breath, chest pain, cough, blood-stained sputum and transient loss of consciousness (6). However, these symptoms are neither indicative nor specific for PE. Therefore, prompt patient evaluation for the probability of PE is paramount and can be done by clinical judgement or through use of a validated prediction rule. The probability of PE will guide the choice of further diagnostic tests (8).

The Wells and Geneva clinical probability assessment scoring systems are used for the classification of a patient’s probability of PE based on clinical criteria (10, 11); revised versions simplify the probability assessments (Table 1) (8, 12, 13). In both systems, points are assigned based on specific clinical features that can be assessed easily (Table 1). The PE Wells score has a range of 0–12.5 points: in the three-tiered scheme, ≤1, 2–6 and ≥7 points indicate low, intermediate and high probability of PE, respectively; in the two-tiered scheme, 0–4 points indicate that PE is unlikely and ≥5 points indicate that PE is likely (Table 1) (8, 12). Both the two- and three-tiered Wells scoring systems have been validated extensively (14–18). The Geneva system has a score range of 0–25 points: in the three-tiered scheme, patients are classified as having low, medium or high probability of PE if they score ≤3, 4–10 or ≥11 points: in the two-tiered scheme, 0–5 points indicates PE is unlikely and ≥6 points indicates that PE is likely (8, 13). Independent of which method is used, approximately 10%, 30% and 65% of patients fall into the low-, intermediate- and high-probability categories, respectively (8).

Diagnosis of PE

No individual test conclusively excludes or confirms PE diagnosis. Diagnosis, therefore, depends on a
combination of clinical assessment, laboratory tests and imaging methods. The choice of diagnostic tests depends on the clinical probability of PE, the availability of tests, the medical condition of the patient, the risks of iodinated contrast material and radiation exposure, and the cost of procedures (8).

The D-dimer test is a standard blood test. Activation of the coagulation cascade and fibrinolysis cause elevated D-dimer levels, which may indicate the presence of a blood clot. Therefore, in patients with a low-to-moderate pre-test probability of PE, a negative D-dimer test excludes a PE diagnosis. A positive D-dimer test in this patient group is not synonymous with a PE, because of its low specificity, but indicates the need for further diagnostic tests. Patients with a high pre-test probability will require imaging to exclude or confirm the diagnosis of PE (8).

A diagnosis of PE is typically confirmed by computed tomographic pulmonary angiography (CTPA), spiral computed tomography, a high-probability ventilation-perfusion (V/Q) scintigraphy scan or pulmonary angiography. CTPA is the gold standard for first-line imaging of patients with suspected PE because it is sensitive, non-invasive and relatively cheap. However, in some patient groups, including those with severe renal insufficiency or allergy to contrast media and in pregnant women, CTPA should be used with caution (8, 19), and alternative (albeit more expensive) diagnostic strategies, such as V/Q scanning, should be considered.

The key clinical consequences of a PE are of a haemodynamic nature. Clinical assessment of haemodynamic status is used to evaluate the severity of PE (8). To assess haemodynamic status or right ventricular function, echocardiography, computed tomography, measurement of cardiac biomarkers (serum troponins, brain natriuretic peptides) and lower-limb compression ultrasound to detect concurrent DVT may be used.

### Risk stratification

Rapid risk stratification and prompt treatment are paramount because of the high mortality rate associated with PE (20). Although clinical severity is usually associated with the size of the embolus and the degree of vessel occlusion, anatomically massive PE is not synonymous with clinically massive PE (21). Anatomically massive PE can sometimes occur with few signs or symptoms, whereas co-morbidities, age and medical

| Table 1. Clinical prediction rules for pulmonary embolism according to the Wells and Geneva scores (8) |
|---|---|---|---|---|---|
| **Wells score** | **Points** | **Revised Geneva score** | **Points** |
| **Predisposing factors** | | **Predisposing factors** | | **Points** |
| Previous DVT or PE | +1.5 | Age >65 years old | +1 |
| Recent surgery or immobilisation | +1.5 | Previous DVT or PE | +3 |
| Active cancer | +1 | Surgery or fracture within 1 month | +2 |
| **Symptoms** | | Active cancer | +2 |
| Haemoptysis | +1 | Unilateral lower-limb pain | +3 |
| Clinical signs | | Haemoptysis | +2 |
| Heart rate >100 beats/min | +1.5 | Heart rate 75–94 beats/min | +3 |
| ≤95 beats/min | +5 | Pain on lower-limb deep vein at palpation and unilateral oedema | +4 |
| Clinical signs of DVT | +3 | Clinical signs | |
| **Clinical judgement** | Alternative diagnosis less likely than PE | +3 |

| Clinical probability (three-tier) | Total | Clinical probability (three-tier) | Total |
|---|---|---|---|
| Low | 0–1 | Low | 0–3 |
| Intermediate | 2–6 | Intermediate | 4–10 |
| High | ≥7 | High | ≥11 |

| Clinical probability (two-tier) | Clinical probability (two-tier) |
|---|---|
| PE unlikely | 0–4 | PE unlikely | 0–5 |
| PE likely | ≥5 | PE likely | ≥6 |

DVT, deep vein thrombosis; PE, pulmonary embolism.
status of the patient may transform a relatively small embolus, involving limited lung segments, into a clinically serious condition (21).

Patients presenting with suspected PE who are haemodynamically unstable (with cardiogenic shock or persistent hypotension) should immediately be stratified as high risk prior to any diagnostic work-up. For haemodynamically stable patients, risk stratification, according to the expected PE-related risk of early death, should take place once PE diagnosis is confirmed to ensure appropriate treatment. Multiple risk-stratification scoring systems exist to forecast outcomes in patients with acute PE, including the Pulmonary Embolism Severity Index (PESI), simplified PESI and the Prognosis in Pulmonary Embolism (PREP) scores (Table 2) (22–24).

The PESI is a reproducible scoring system that predicts 30-day mortality risk (22, 25) based on 11 patient characteristics, including age, male sex, three co-morbid illnesses (cancer, heart failure, chronic lung disease) and six clinical findings (pulse ≥110 beats/min, systolic blood pressure <100 mmHg, respiratory rate ≥30 breaths/min, body temperature <36°C, altered mental status and oxygen saturation <90%). Points are assigned for each of these variables. The original PESI system (Table 2) stratifies patients into five risk classes including very low (≤65 points), low (66–85 points), intermediate (86–105 points), high (106–125 points) and very high (>125 points) risk (22). Owing to the complexity of the original PESI, a simplified PESI has been introduced (23). In the simplified PESI score, one or more of the following variables equates to a high risk of PE: age >80 years, history of cancer or chronic cardiopulmonary disease, high heart rate (pulse ≥110 beats/min), low blood pressure (systolic blood pressure <100 mmHg) and arterial oxyhaemoglobin saturation <90% (Table 2). The PREP score is an abridged version of the PESI score and is based on only three clinical variables, namely presence of altered mental status, cardiogenic shock and cancer, as well as echocardiographic and biochemical variables (Table 2) (24). Patients are categorised as having a low or a high risk of death according to their PREP score (26).

These prediction rules can be used to provide guidance for the most appropriate treatment intervention and also for identifying low-risk patients for whom home treatment may be suitable. According to the European Society of Cardiology (ESC) guidelines, patients with an intermediate risk of mortality of 3%–15% should be admitted to hospital, whereas patients with a mortality risk of <1% can be considered for home treatment (27).

Table 2. Variables and points system used to calculate the Pulmonary Embolism Severity Index (PESI) score (original and simplified PESI) and the Prognosis in Pulmonary Embolism (PREP) score for the assessment of pulmonary embolism probability (22–24)

| Variable | Original PESI | Simplified PESI | PREP |
|----------|---------------|----------------|------|
| Age      | Age, in years | (>80 years) +1 |      |
| Male sex | +10           |                |      |
| Altered mental status | +60 | +10 |
| History of cancer | +30 | +1 | +6 |
| History of heart failure | +10 | +1* |
| History of chronic lung disease | +10 | |
| Temperature <36°C | +20 | |
| Brain natriuretic peptide | +20 | |
| Pulse ≥110 beats/min | +1 | +1–8† |
| Systolic blood pressure <100 mmHg | +30 | +1 |
| Cardiogenic shock on admission | +20 | +6 |
| Respiratory rate ≥30 breaths/min | +20 | +3–11‡ |
| Arterial oxyhaemoglobin saturation level <90% | +20 | +1 |

| Risk classification | Very low (≤65) | Low (66–85) | Intermediate (86–105) | Low (0) | Low (≤6) | Intermediate (7–17) | High (106–125) | High (≥1) | High (≥18) |
|---------------------|----------------|-------------|----------------------|--------|---------|---------------------|----------------|-------------|-----------|

*Merged into one category: chronic cardiopulmonary disease.
†1100–249 ng/L (+1), 250–499 ng/L (+2), 500–999 ng/L (+4), ≥1000 ng/L (+8).
‡0.5–0.74 (+3), 0.75–1.00 (+5), 1.00–1.25 (+8), ≥1.25 (+11).
Current treatment strategies

Evidence-based guidelines for anticoagulation treatment of acute PE have been published by the ESC (8) and the American College of Chest Physicians (9). The treatment approach for acute PE is dependent on risk stratification of the individual patient.

In haemodynamically stable patients, anticoagulation with dual-drug strategies, involving acute phase parenteral anticoagulation [with low molecular weight heparin (LMWH), fondaparinux or unfractionated heparin (UFH)], overlapping with and followed by VKA therapy, is recommended (8, 9); dabigatran is recommended as an alternative to VKA treatment (8, 9).

As an alternative to dual-drug therapy, single-drug therapy with apixaban (8) or rivaroxaban (8, 9) is recommended with an initial intensified treatment regimen; this approach avoids the need for parenteral administration, which is considered to be inconvenient in some patients. The use of DOACs for longer-term anticoagulation in the place of VKAs overcomes many of the limitations associated with VKA therapy, including the need for regular coagulation monitoring [every 2–6 weeks after stable international normalised ratio (INR) has been achieved] and dose adjustments with VKAs to maintain the target INR. In addition, VKAs exhibit over 200 drug and dietary interactions (28).

In some countries, patients only spend approximately 40% of time within the target therapeutic window, suggesting suboptimal anticoagulation (29, 30), although other countries have reported higher percentages of over 65% (31–33). Inferior vena cava filters may be used in patients in whom anticoagulation has failed or who have contraindications to anticoagulation; however, their routine use is not recommended (8).

The timing of anticoagulation initiation is mainly influenced by how soon diagnostic testing can be performed and the patient’s risk of bleeding (8, 34). In patients with a high clinical suspicion of PE, anticoagulation treatment is initiated immediately, prior to diagnostic confirmation. In patients with an intermediate level of clinical suspicion, initiation of anticoagulation is recommended if results of diagnostic tests are delayed for more than 4 h. In patients with low clinical suspicion, anticoagulation may be delayed until confirmation of diagnosis (if expected within 24 h) (9).

In high-risk haemodynamically unstable PE patients, anticoagulation therapy with apixaban or rivaroxaban is not recommended (35, 36), and anticoagulation therapy with intravenous UFH should be initiated without delay (8, 9). In these patients, restoration of pulmonary arterial flow is urgently required because of the risk of right ventricular failure. Thrombolytic therapy with streptokinase, urokinase or recombinant tissue plasminogen activator is therefore recommended as an immediate treatment strategy (8, 9). In patients in whom thrombolitics are contraindicated, catheter-assisted thrombus removal or surgical pulmonary embolectomy may be considered. Owing to the high periprocedural risk, the latter is only indicated in patients in whom thrombolysis is contraindicated or has failed, or shock is likely to cause death before thrombolysis can take effect (8, 9).

Evidence supporting the use of DOACs for the treatment of PE

The approvals of rivaroxaban and apixaban (as single-drug therapies) and of dabigatran (as a dual-drug therapy after 5–10 days of parenteral therapy) in the European Union and United States for the treatment of acute DVT or PE and prevention of recurrent DVT or PE were based on the results of randomised phase III clinical trials (37–41). Edoxaban has also been assessed in a phase III study in this indication (42). The study design of these trials differed in some key features (Table 3) (37–42). For example, whereas EINSTEIN DVT and EINSTEIN PE were open-label studies, the other trials had a double-blind design. Rivaroxaban in the EINSTEIN studies and apixaban in the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) study were given as single-drug therapies from the initiation of treatment, whereas dabigatran in the RE-COVER studies and edoxaban in the Hokusai-VTE study were given after initial parenteral treatment (Table 3). Moreover, in contrast to the EINSTEIN DVT and EINSTEIN PE studies, phase III studies with other DOACs included mixed populations of DVT and PE patients (Table 4) (37–42).

Rivaroxaban is the only DOAC that has been assessed in two separate phase III studies for the treatment of acute DVT and PE (EINSTEIN DVT and EINSTEIN PE) (37, 38). In both studies, patients received either rivaroxaban as a single-drug therapy (15 mg twice daily for the first 3 weeks followed by 20 mg once daily) or body weight-adjusted, subcutaneous enoxaparin twice daily together with an oral VKA, followed by a VKA alone once the INR was within the therapeutic range (2.0–3.0) (37, 38). Intensive rivaroxaban treatment for the first 3 weeks in patients with VTE has demonstrated effective clot resolution and ensures that patients are adequately protected when they are at most risk of recurrent events (43–45). Patients in the EINSTEIN DVT and EINSTEIN PE studies were treated for 3, 6 or 12 months (37, 38).
Table 3. Key features of study designs of the phase III venous thromboembolism treatment studies with direct oral anticoagulants (40–42, 50)

| AMPLIFY | EINSTEIN pooled* | Hokusai-VTE | RE-COVER pooled |
|---------|------------------|-------------|-----------------|
| Randomised patients, n | 5395 | 8282 | 8292 | 5107 |
| Drugs compared | Apixaban vs enoxaparin/VKA | Rivaroxaban vs enoxaparin/VKA | Heparin/edoxaban vs heparin/warfarin | Heparin/dabigatran |
| Study design | Double-blind | Open-label, assessor-blind | Double-blind | Double-blind |
| Statistical outcome | Non-inferiority | Non-inferiority | Non-inferiority | Non-inferiority |
| Treatment regimen for DOAC | 10 mg bid for 7 days followed by 5 mg bid | 15 mg bid for 3 weeks followed by 20 mg od tablets† | 60 mg od (2 × 30 mg tablets)† | 150 mg bid |
| Treatment duration (months) | 6 | 3, 6 or 12 | 3–12 | 6 |

*EINSTEIN DVT and EINSTEIN PE had the same study design.
†A reduced dose was given to patients with a creatinine clearance of 30–50 mL/min, a body weight of <60 kg or to patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors.

EINSTEIN PE assessed outcomes in patients with PE with or without DVT. Rivaroxaban was non-inferior to enoxaparin/VKA for the prevention of symptomatic recurrent VTE (2.1% vs 1.8%; P = 0.003) with similar rates of major and non-major clinically relevant bleeding (10.3% vs 11.4%; P = 0.23). Rates of major bleeding were significantly lower in the rivaroxaban group (1.1% vs 2.2%; P = 0.003) (Table 5) (38, 42). Importantly, rivaroxaban was associated with fewer fatal bleeding events and intracranial haemorrhages compared with enoxaparin/VKA. Overall, the EINSTEIN PE study demonstrated that rivaroxaban offers a viable alternative to standard of care treatment in patients with acute PE (38).

Apart from efficacy and safety, length of hospital stay (contributing to the overall cost of patient care) and patient satisfaction (associated with patient adherence to a drug) are also important factors that influence treatment decisions and patient outcomes. Additional analyses of data from the EINSTEIN PE study found that patients with PE treated with rivaroxaban spent significantly less time in hospital (46) and reported significantly higher treatment satisfaction (47) than those treated with enoxaparin/VKA.

The other DOACs, which have been evaluated in phase III trials for the treatment of acute VTE, included mixed DVT and PE patient populations. The number of patients with acute PE included in these studies differed greatly (Table 4). Here, we will focus only on outcomes reported for patients with PE (Table 5). Dabigatran was assessed in two phase III trials (RE-COVER and RE-COVER II). In both studies, all patients initially received heparin treatment (UFH or LMWH) for a median of 9.0 days in RE-COVER and 9.6 days in RE-COVER II. Heparin therapy occurred in parallel with the initiation of dose-adjusted warfarin (target INR of 2.0–3.0) or before initiation of dabigatran 150 mg twice daily (Table 3) (39, 40). Treatment duration was 6 months (39, 40). In a pooled analysis of these two trials, the incidence of recurrent symptomatic VTE and VTE-related death was similar in both treatment arms for patients with PE [2.3% vs 2.6%; hazard ratio (HR); 95% confidence interval (CI) not reported] (40). Safety outcomes were not reported for the subgroup of patients with PE in these studies (Table 5) (39, 40). Dual-drug therapy with dabigatran is also expected to improve treatment satisfaction, but data are not yet available.

Hokusai-VTE, a dual-drug study of the treatment of acute VTE, compared the efficacy and safety of edoxaban with warfarin after initial treatment with heparins for a median of 7 days in both treatment arms (42). The treatment groups received edoxaban (60 mg once daily) or dose-adjusted warfarin with a target INR of 2.0–3.0 (Table 3). A reduced dose of edoxaban 30 mg once daily was given to patients with a creatinine clearance (CrCl) of 30–50 mL/min, a body weight of <60 kg or to patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors (42). In patients with PE, edoxaban was non-inferior to warfarin for the prevention of recurrent symptomatic VTE (2.8% vs 3.9%; HR = 0.73, 95% CI 0.50–1.06) (Table 5). Rates of major and non-major clinically relevant bleeding events (defined as the principal safety outcome) were similar in both treatment arms (10.1% vs 11.2%; HR and 95% CI not reported) (42).

The AMPLIFY study compared apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) as a single-drug therapy with enoxaparin/VKA therapy for 6 months in patients with acute VTE (Table 3) (41). In patients with PE, apixaban was non-inferior to enoxaparin/VKA for the prevention of recurrent symptomatic VTE and VTE-related death (2.3% vs 2.6%; relative risk = 0.9, 95% CI 0.5–1.61), and was
Table 4. Initial diagnosis of pulmonary embolism as the index event in phase III studies with direct oral anticoagulants (37–42)

| AMPLIFY | EINSTEIN DVT/EINSTEIN PE* | Hokusai-VTE | RE-COVER | RE-COVER II |
|---------|--------------------------|-------------|----------|------------|
| Apixaban | Enoxaparin/ warfarin | Rivaroxaban | Enoxaparin/ VKA | Heparin/ edoxaban | Heparin/ warfarin | Heparin/ dabigatran | Heparin/ warfarin | Heparin/ dabigatran |
| N       | 2691                     | 2704        | 4151     | 4131       | 4118          | 4122          | 1273       | 1266       | 1280       | 1288 |
| PE only, n (%) | 678 (25.2) | 681 (25.2) | 1813 (43.7) | 1823 (44.1) | – | – | 270 (21.2) | 271 (21.4) | 298 (23.3) | 297 (23.1) |
| PE with DVT, n (%) | 252 (9.4) | 225 (8.3) | 606 (14.6) | 590 (14.3) | 410 (10.0) | 404 (9.8) | 121 (9.5) | 124 (9.8) | 104 (8.1) | 117 (9.1) |
| PE with or without DVT, n (%) | – | – | 2431 (58.6) | 2424 (58.7) | 1650 (40.1) | 1669 (40.5) | – | – | – | – |
| Could not be evaluated, n (%) | 12 (0.4) | 15 (0.6) | – | – | – | – | 2 (0.2) | 2 (0.2) | 1 (0.1) | 1 (0.1) |

*EINSTEIN DVT included a small number of patients with PE only as the index event (12 patients in the rivaroxaban arm and 11 patients in the enoxaparin/VKA arm).

DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonist.

Table 5. Results from the acute venous thromboembolism studies – subgroup of PE patients (index event PE ± deep vein thrombosis) (38, 40–42)

| AMPLIFY | EINSTEIN PE | Hokusai-VTE* | RE-COVER pooled |
|---------|-------------|--------------|-----------------|
| Apixaban | Enoxaparin/ warfarin | Rivaroxaban | Enoxaparin/VKA | Heparin/edoxaban | Heparin/warfarin | Heparin/dabigatran | Heparin/warfarin |
| Primary efficacy endpoint | First recurrent symptomatic VTE or VTE-related death | Recurrent symptomatic VTE: composite of fatal or non-fatal PE or DVT | Recurrent symptomatic VTE: composite of DVT or non-fatal or fatal PE | Recurrent symptomatic objectively confirmed VTE and related deaths |
| Definition | | | | |
| n/N (%) | 21/900 (2.3) | 23/886 (2.6) | 47/1650 (2.8) | 18/795 (2.3) |
| HR/RR (95% CI) | RR = 0.90 (0.50–1.61) | HR = 1.12 (0.75–1.68) | HR = 0.73 (0.50–1.06) | NR |
| Major bleeding | | | | |
| n/N (%) | 4/928 (0.4) | 25/902 (2.8) | 52/2405 (2.2) | NR |
| HR/RR (95% CI) | NR | HR = 0.49 (0.31–0.79) | NR | NR |

*Modified intention-to-treat and safety analysis.

CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; NR, not reported; PE, pulmonary embolism; RR, relative risk; VKA, vitamin K antagonist; VTE, venous thromboembolism.
associated with significantly lower rates of major bleeding events (primary safety outcome; 0.4% vs 2.8%; relative risk and 95% CI not reported) (Table 5).

Some patient subgroups, such as patients who are elderly or those with renal impairment or cancer, have a high risk of bleeding in addition to a high risk of recurrent VTE. Therefore, physicians may be reluctant to prescribe VKAs because of their association with an increased risk of major bleeding and intracranial haemorrhage (28, 48, 49). The phase III studies that assessed the DOACs for the treatment of acute VTE reported outcomes in these subgroups in mixed populations of DVT and PE patients. In a pooled analysis of the EINSTEIN DVT and EINSTEIN PE data, rivaroxaban showed similar efficacy and significantly lower rates of major bleeding events compared with enoxaparin/VKA in fragile patients (defined as age ≥75 years, CrCl ≤50 mL/min or body weight ≤50 kg) (50). In fragile patients from the Hokusai-VTE study (defined as age ≥75 years, body weight ≤50 kg or CrCl ≥30–≤50 mL/min), heparin/edoxaban treatment was associated with significantly lower rates of recurrent VTE and similar rates of major plus non-major clinically relevant bleeding compared with heparin/warfarin (42). In the AMPLIFY study, subgroup analyses, including analyses according to age or CrCl, demonstrated similar efficacy compared with enoxaparin/warfarin. Rates of major bleeding events were significantly lower in elderly patients (age ≥75 years) receiving apixaban compared with those receiving enoxaparin/warfarin (41). Similar efficacy outcomes for heparin/dabigatran compared with heparin/warfarin were reported for various subgroups including age, weight, active cancer and CrCl in the pooled RE-COVER and RE-COVER II analysis (40, 51, 52). Moreover, the number of bleeding events in patients with active cancer, in patients with mild (CrCl >50–<80 mL/min) or moderate (CrCl ≥30–≤50 mL/min) renal impairment, or in elderly subgroups (age groups: 65–75 years, >75 years or ≥80 years) were similar or numerically lower for heparin/dabigatran compared with heparin/warfarin (51–53).

Conclusions
Prompt diagnosis and treatment of PE are crucial for optimising patient outcomes. Risk stratification for early mortality risk guides treatment decisions in patients with PE, and initiation of anticoagulation is recommended in all haemodynamically stable patients. Traditional dual-drug therapy is associated with potential limitations. Of the DOACs, rivaroxaban, apixaban and dabigatran etexilate are approved in Europe and the United States for the treatment of acute DVT or PE and prevention of recurrent DVT or PE. Edoxaban is approved in the United States but not currently in the European Union for the treatment of DVT and PE; approval of edoxaban in Europe is anticipated in the near future. Rivaroxaban and apixaban offer a single-drug approach and dabigatran a dual-drug approach (after 5–10 days of initial parenteral anticoagulation) in this indication. All three approved DOACs have multiple advantages over traditional therapies, including a fast onset of action, convenient oral administration, a fixed daily dosing regimen, predictable pharmacokinetic and pharmacodynamic effects (and, therefore, no need for regular coagulation monitoring), and no food and only minimal drug interactions. Rivaroxaban has a very similar pharmacokinetic profile to enoxaparin, including onset of action and time to peak plasma concentration (54). Similar to rivaroxaban, other DOACs also exhibit a fast onset of action (55). Therefore, the sometimes-held belief that an injectable agent is a faster acting and a more efficient option than an oral drug is invalid.

Single-drug therapy with rivaroxaban or apixaban may also simplify the management of VTE treatment and hospital-to-home transition for patients. Patients who were treated with rivaroxaban had shorter hospital stays and higher treatment satisfaction than those treated with conventional dual-drug therapy. The improved treatment satisfaction with rivaroxaban as perceived by patients may increase adherence to treatment, which in turn may result in improved health outcomes. Similarly, treatment with apixaban or dabigatran is also expected to improve treatment satisfaction, but data are not yet available. Introduction of the DOACs in clinical practice is likely to assist physicians in optimising treatment of patients with PE and in improving clinical outcomes.

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