ESC European Society of Cardiology
European Heart Journal - Show Case
doi:10.1093/ehjcr/ytaa542

CLASSIC CASE REPORT
Other

The 2019 European guidelines on pulmonary embolism illustrated with the aid of an exemplary case report

Andrea Gallo[1,2], Luca Valerio [1], and Stefano Barco [1,3]

[1]Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Langenbeckstraße 1, Building 403, Room 117, 55131 Mainz, Germany; [2]Department of Medicine and Surgery, Research Centre on Thromboembolic Diseases and Antithrombotic Therapies, University of Insubria, Varese, Italy; and [3]Clinic of Angiology, University Hospital Zurich, Zurich, Switzerland

Received 28 June 2020; first decision 2 September 2020; accepted 4 December 2020

Background The European Society of Cardiology guidelines for the diagnosis and management of acute pulmonary embolism (PE) developed in collaboration with the European Respiratory Society (ERS) has been updated in 2019. Recommendations were added or updated on all stages of the evaluation and management of pulmonary embolism, encompassing diagnosis, early treatment, and long-term management.

Case summary We illustrate an exemplary case, assembled for the purposes of this review, of a 70-year-old woman who presented at the emergency department with dyspnoea and thoracic pain. She was diagnosed with intermediate–high-risk acute PE and promptly treated with low molecular weight heparin. After 24 h of stay in intensive care unit, she was transferred to the cardiology department and switched to non-vitamin K-dependent oral anticoagulant apixaban 10 mg b.i.d. for 7 days and then 5 mg b.i.d. After discharge from the hospital 8 days later, she received standard-dose apixaban 5 mg b.i.d. for 6 months; the dose was reduced to 2.5 mg b.i.d. for long-term secondary prevention. During follow-up, investigations for PE sequelae were performed due to persisting dyspnoea.

Discussion This exemplary case report puts into context the main novel recommendations from the 2019 ESC Guidelines, including the combination of clinical (pre-test) probability and adjusted D-dimer cut-offs for diagnosis of acute PE, the key role of right ventricular dysfunction in risk stratification, the choice and dosage of oral anticoagulant agents in early and extended anticoagulation, and the identification and management of chronic sequelae in the long-term follow-up.

Keywords Pulmonary embolism • Guidelines • Venous thromboembolism • Anticoagulation • Case report

Learning points

- The diagnosis of acute pulmonary embolism (PE) is based on the combination of clinical pre-test probability, D-dimer levels, and imaging tests.
- The assessment of right ventricular function is key in risk stratification of patients with acute PE.
- Non-vitamin-K-dependent oral anticoagulants (NOACs) became the drug of choice for the early and the extended anticoagulant treatment in most patients with PE.
- Post-PE care and long-term follow-up represent a crucial part of PE management.

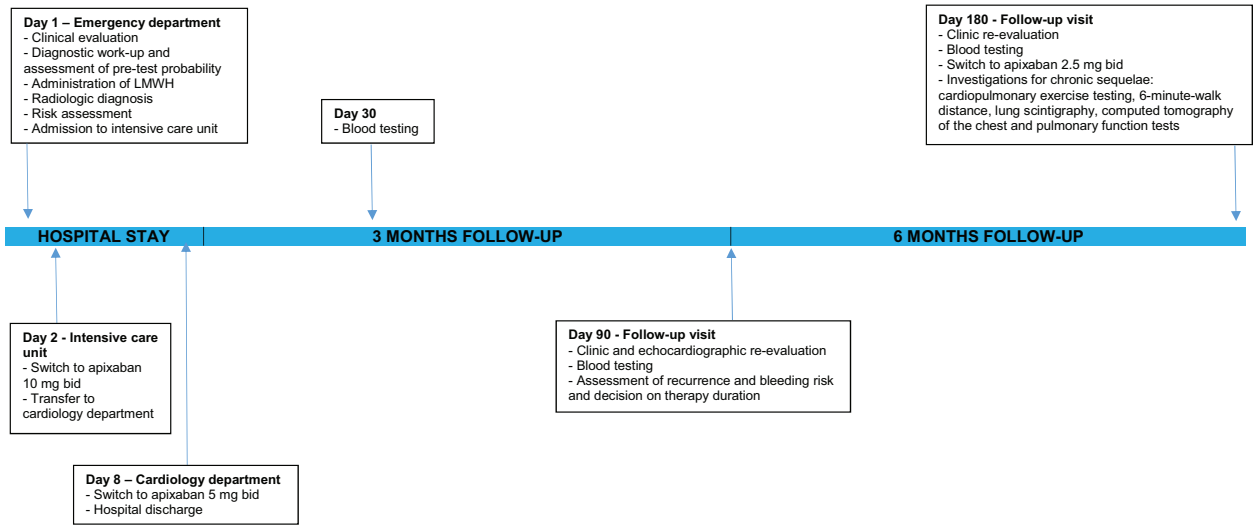
* Corresponding author. Tel: +41 (0) 432531150, Fax: +49 6131 17 8461, Email: stefano.barco@usz.ch
Handling Editor: Tom De Potter
Peer-reviewers: Dmitry Duplyakov and Dan Octavian Nistor
Compliance Editor: Alexander Tindale
Supplementary Material Editor: Deepti Ranganathan

Introduction

In 2019, the European Society of Cardiology (ESC), developed with the endorsement of the European Respiratory Society (ERS), published the new guidelines for the diagnosis and management of acute pulmonary embolism (PE)[1] updating the previous version from 2014.[2]

In this article, we present an exemplary case of acute PE with the aim of putting into context and discussing some of the novel recommendations concerning PE management from the 2019 ESC Guidelines. The updates most likely to affect clinical practice include the combination of clinical (pre-test) probability and adjusted D-dimer cut-offs for diagnosis, the role of right ventricular dysfunction in risk stratification, the choice and dosage of oral anticoagulant agents in early and extended anticoagulation, and the identification and management of chronic sequelae in the long-term follow-up. The readers will follow the case as it unfolds with each clinical decision accompanied by a discussion of the recommendations supporting it.

Timeline



Case presentation

A 70-year-old non-smoker Caucasian woman with arterial hypertension presented with a two-day history of dyspnoea and thoracic pain. Her blood pressure was 130/65 mmHg; heart rate was 112 beats per minute; peripheral oxygen saturation was 98% on room air and the respiratory frequency was 36/min. The remainder of her physical examination was normal, including soft, non-tender calves; her body weight was 75 kg. She described the chest pain as moderate and exacerbated by deep breathing. Dyspnoea was present at rest at the time of evaluation. Two weeks before, she had suffered an ankle sprain that required bed rest with bathroom privileges for a few days. The patient denied any previous personal or family history of venous thromboembolic (VTE) events or any additional risk factors for VTE.

Routine tests included electrocardiogram (sinus tachycardia with negative T waves V2-V4), chest X-ray (normal findings), arterial blood gas (pO2 59 mmHg, pCO2 32 mmHg, normal pH and bicarbonate level). High-sensitivity troponin T was 52 ng/mL (normal range: <14 ng/mL) and NT-proBNP was 610 pg/mL (normal reference range <100 pg/dL).

The physicians at the Emergency Department calculated the Wells score, which was 3 (1.5 points for immobilization and 1.5 for tachycardia), indicating an intermediate pre-test probability of PE, Therefore, a D-dimer test was performed that returned a level of 1060 ng/mL (normal reference range <500 ng/mL). Administration of low-molecular-weight heparin (LMWH) at therapeutic dose was promptly started.

The diagnostic workup of PE without haemodynamic instability begins with the assessment of the patient's clinical (pre-test) probability of PE, which encompasses a combination of clinical findings and the evaluation of predisposing factors for venous thromboembolism (VTE). The Wells and the Geneva score, or their simplified versions, are simple and extensively validated prediction rules to assess the patient's probability of having acute PE.[3,4] Specifically, the Wells score includes seven items regarding clinical history, symptoms, and signs suggestive of deep vein thrombosis (DVT) or PE. The 2019 ESC Guidelines endorse their use with a recommendation Class I and a level of evidence B (I, B). Their assessment serves to (i) initiate anticoagulation without any delay in patients with high or intermediate clinical probability of PE (I, C); (ii) perform an imaging test in patients with a high or intermediate clinical probability of PE; (iii) test D-dimer

levels in patients with a low clinical probability, in order to decide whether to perform computed tomography pulmonary angiography (CTPA) or a ventilation-perfusion (V/Q) lung scan.

In case of low or intermediate clinical probability of PE, guidelines recommend plasma D-dimer measurement (I, A). In contrast, D-dimer testing is not recommended in patients with high clinical probability of PE as a normal test does not safely exclude PE (III, A) and, therefore, a CTPA or a V/Q lung scan should be done without delay.

> *As the D-Dimer was above the age-adjusted cut-off of 700 ng/nL (for a patient aged 70 years), the physicians decided to perform an urgent CTPA. The CTPA showed multiple bilateral segmental pulmonary emboli and right ventricle enlargement.*

A novelty of the 2019 ESC guidelines is the introduction of two alternatives (both rated as IIa, B) to a fixed D-dimer cut-off with the aim of increasing the specificity of D-dimer testing without affecting its sensitivity, thus reducing the number of patients unnecessarily undergoing CTPA. The first alternative is an age-adjusted D-dimer cut-off (age × 10 mg/L, in patients aged >50 years), the second is the YEARS decision rule, which adapts the D-dimer cut-off measured at the time of clinical assessment to the clinical probability as assessed by a simplified Wells score with only three items.[5,6]

Computed tomography pulmonary angiography is the imaging method of choice in patients with suspected PE.[7] Pre-test clinical probability heavily influences both its negative and its positive predictive value. Accordingly, guidelines recommend rejecting the diagnosis PE if CTPA is normal in patients with a low or intermediate clinical probability of PE (I, A), accepting the diagnosis of PE if CTPA is positive in patients with an intermediate or high clinical probability (I, B).

The possibility of findings supporting alternative diagnoses is an advantage of CTPA over other imaging modalities. However, a study on patients undergoing CTPA for suspected PE found that findings supporting an alternative diagnosis only rarely had therapeutic consequences.[8] Therefore, physicians should be aware that an inappropriate use of CTPA without a solid diagnostic work-up may have a limited value in the global management of the patient.

> *The echocardiogram confirmed right ventricle enlargement (RV/LV: 1.1 with a normal range considered to be below 1.0) with increased systolic pulmonary arterial hypertension (PAPs: 42 mmHg), decreased tricuspid systolic velocity (TAPSE; 14 mm) and decreased tricuspid annular peak systolic (S') velocity (<9.5 cm/s) on tissue Doppler imaging; McConnell's sign was absent while the 60/60 sign was positive. The patient was admitted to the intensive care unit (ICU) for 24-hour monitoring.*

Diagnosis of PE must be accompanied by risk stratification: the risk categories are high risk, intermediate risk (further distinguished into intermediate-low and intermediate-high risk), and low risk.

Haemodynamic instability, defined as the presence of cardiac arrest, obstructive shock, or persistent hypotension, identifies high-risk patients, which must be monitored in an intensive care unit.

In patients without haemodynamic instability, further stratification into intermediate or low-risk categories is recommended by the guidelines as a next step (I, B) based on clinical prediction rules such as the Pulmonary Embolism Severity Index (PESI) or its simplified version (sPESI; IIa, B). Overall, a PESI of Class I–II is a reliable predictor of low-risk PE. Echocardiography or CTPA can identify signs of right ventricular (RV) dysfunction the findings most frequently associated with unfavourable prognosis include a right ventricular/left ventricular diameter ratio (RV/LV) ≥ 1.0 and a TAPSE < 16 mm.[9,10] Plasma levels of troponin and N-terminal (NT)-proBNP are markers of myocardial injury and RV pressure overload, respectively.[11,12] Patients in the intermediate-risk group who display evidence of both RV dysfunction on imaging and elevated cardiac biomarker levels are classified into the intermediate–high-risk category. These patients should be monitored in an intensive care unit to permit the early detection of haemodynamic decompensation or collapse, so that appropriate measures can be taken promptly (I, B). Conversely, patients with no signs of RV dysfunction and/or normal cardiac biomarker levels belong to the intermediate–low-risk category; these patients do not require monitoring in an intensive care unit but should be hospitalized.

Selected patients with low-risk PE should be considered for early discharge and home anticoagulant treatment. Purely clinical assessment tools, such as the PESI, evaluate PE-related complications or comorbidities. Tools such as the Hestia exclusion criteria also include the patient's expected compliance, family, and social environment, as well as the local coordination between primary and secondary care. The recommendation of home treatment for selected patients remains unchanged from the 2014 ESC guidelines, but its grade was increased on account of the results of the international investigator-initiated Home Treatment of patients with acute PE (HoT-PE) phase IV trial[13] and of a meta-analysis of observational studies showing that in low-risk patients with acute PE classified based on clinical scores alone, the absence of RV dysfunction on admission on top of other clinical criteria was associated with a negligible rate of early PE-related complications and death[14]. In line with this principle, the guidelines specify that assessment of RV function should be included in the risk stratification of all patients with acute PE if early discharge is considered.

> *During ICU stay, rescue thrombolytic therapy was not necessary. After transferral to the cardiology ward, she was switched to the non-vitamin K-dependent oral anticoagulant (NOAC) apixaban at a dosage of 10 mg twice daily, based on her body weight of 75 kg and an estimated glomerular filtration rate of 69 mL/min. A compression ultrasound of the lower limb excluded DVT.*

The 2019 ESC guidelines confirm previous recommendations to reserve systemic thrombolytic therapy to high-risk patients (I, B). Surgical pulmonary embolectomy (I, C) or percutaneous catheter-directed treatment (IIa, C) are recommended if thrombolysis is contraindicated or has failed. In intermediate-risk patients, the clinical benefit of systemic thrombolysis is absent due to the substantial bleeding rate of this treatment strategy.[15] Therefore, guidelines discourage routine use for these patients (III, B).

In all patients, anticoagulation therapy should be started. The optimal anticoagulant in the early stages depends on the risk group. Immediate start of unfractionated heparin (UFH) is recommended in high-risk patients (I, B) because its anticoagulant effect can be easily monitored and rapidly reversed by protamine.[16] Notably, in the PEITHO study LMWH or fondaparinux were administered before randomization in 30.1% of patients.[15]

In all other patients, physicians can choose primarily oral anticoagulation using one of the non-vitamin K antagonist oral anticoagulants (NOAC) apixaban or rivaroxaban with an increased initial dose of apixaban for 7 days[17] or rivaroxaban for 21 days.[18] If physicians choose initial parenteral anticoagulation, LMWH or fondaparinux are recommended over UFH for patients without severe renal impairment [creatinine clearance (CrCl) ≤ 30 mL/min] or severe obesity (I, A). When initiating oral anticoagulation, the 2019 ESC Guidelines now recommend that a NOAC be preferred to a vitamin K antagonist (VKA) (I, A). The grade of this recommendation is higher than in the 2014 ESC guidelines where the choice of a NOAC over a VKA was graded I, B.[2]

> *The patient was discharged with no residual dyspnoea after 8 days of hospital stay with the following instruction: continue apixaban 5 mg twice daily; perform routine control of blood cell count, renal and liver function; clinical and echocardiographic assessment after 3 months. In occasion of the latter visit, the patient complained of persisting and progressively worsening exertional dyspnoea* (New York Heart Association – NYHA functional class II–III). *She denied any episode of bleeding during the three months of anticoagulant treatment. The echocardiogram revealed normalized morphology and function of the right heart.*
>
> *The index event was attributed to leg injury (without fracture) with reduced mobility, a minor transient risk factor. Tolerance and compliance to treatment were excellent. No bleeding risk factor was identified. During the control visit, the patient said she was afraid of recurrence.*
>
> *The physicians decided to continue with apixaban 5 mg twice daily for three further months and then reduce the dose to 2.5 mg twice daily for long-term secondary prevention of venous thromboembolism. They noted in the patient's chart that this decision was taken in light of a non-negligible risk of thrombosis recurrence, as the index PE was associated with a minor transient risk factor; a low estimated risk of bleeding under anticoagulation; and the patient's preference. A control visit was planned at 6 months from the index event.*

Therapeutic anticoagulation for at least 3 months is recommended in all patients with PE (1 A), with routine clinical evaluation at 3–6 months after the acute PE episode (I, B).

The optimal duration of anticoagulant treatment after three months should be based on patient's preference and a careful evaluation of the individual concurring risks of recurrence of venous thromboembolism (VTE), which is related to the features of the index PE and bleeding under anticoagulation.

Discontinuation of therapeutic oral anticoagulation after three months is recommended in patients with first PE secondary to a major transient/reversible risk factor (I, B).

Oral anticoagulant treatment of indefinite duration is recommended for patients presenting with recurrent VTE (I, B) and antiphospholipid antibody syndrome (I, B). Patients with this kind of persistent risk factors are considered to be at high risk of recurrence (>8% per year).[19,20]

In all other patients, the risk of VTE recurrence is neither so low nor so high as to permit a one-size-fits-all recommendation concerning extended anticoagulation. The guidelines specify that indefinite anticoagulation should be considered in these patients. This implies that, regardless of the final decision, the underlying rationale should be well documented. In the first instance, this provision applies to patients with a first PE associated with minor transient or reversible risk factors (IIa, C).[19,20] The same recommendation regards patients with a persistent risk factor (IIa, C) and those without identifiable risk factors (IIa, A).

The recommendation to consider indefinite anticoagulation in all patients is based on the superior safety profile of NOACs compared with VKA that was shown in extension trials.[21] If extended oral anticoagulation is chosen, a reduced dose of the NOACs apixaban (2.5 mg twice daily)[22] or rivaroxaban (10 mg once daily)[23] should be considered after 6 months of therapeutic anticoagulation (IIa, A).

Oral anticoagulant treatment with a VKA for an indefinite period is recommended for patients with antiphospholipid antibody syndrome (I, B); cancer-associated VTE is a specific situation discussed in a separate chapter in the guidelines.

In patients who receive extended anticoagulation, the 2019 ESC guidelines recommend reassessment of drug tolerance and adherence, hepatic and renal function, and bleeding risk at regular intervals (I, C).

> *After 6 months from the index event exertional dyspnoea persisted, and no bleeding had occurred. NT-proBNP was within the normal limits and no other laboratories abnormalities were found. Cardiopulmonary exercise testing (CPET) showed reduced maximal aerobic capacity (peak oxygen consumption) and the 6-minute-walk distance was significantly reduced.*
>
> *A V/Q ventilation/perfusion (lung scintigraphy) scan failed to demonstrate any mismatched perfusion defects. Physicians ordered a CT of the chest with both vascular and parenchymal evaluation, which showed a complete recanalization of the pulmonary circle, mild pulmonary emphysema and bronchial disease. Finally, Pulmonary Function Tests (PFTs) revealed a chronic obstructive pulmonary disease (COPD) stage GOLD II. Tiotropium bromide was prescribed with clinical benefit.*

The specifications of the 2019 ESC Guidelines for the long-term management of PE reflect an understanding of PE as a chronic disease. Persisting dyspnoea may be one of the signs of chronic conditions directly related to the underlying thrombo-embolic disorder. Chronic thromboembolic pulmonary hypertension (CTEPH), a life-threatening condition being diagnosed in approximately 3% of PE survivors,[24] is associated with substantial morbidity and mortality and defined by a mean pulmonary arterial pressure of more than 25 mmHg with a pulmonary arterial wedge pressure of less than 15 mmHg, documented at right heart catheterization in a patient with mismatched perfusion defects on V/Q lung scan.[25] Post-PE impairment (PPEI) is an umbrella definition encompassing echocardiographic abnormalities pointing to the presence of pulmonary hypertension combined with a cardiopulmonary symptomatology.[26] Chronic thromboembolic disease (CTED) should be considered in symptomatic patients with documented post-thrombotic obstructions but normal pulmonary haemodynamic parameters at rest and without any other cause of their marked exercise limitation.[27]

Accordingly, further diagnostic evaluation should be considered in patients with persistent or new-onset dyspnoea/exercise limitation after PE (IIa, C). In symptomatic patients with mismatched perfusion defects persisting on V/Q scan beyond 3 months after acute PE, referral to a PH/CTEPH expert centre is recommended, after taking into account the results of echocardiography, natriuretic peptide levels, and/or CPET (I, C).

Lead author biography

Stefano Barco completed his residency in internal medicine at the University of Pavia, Italy, and received a PhD in Vascular Medicine from the University of Amsterdam, the Netherlands. He leads a research group at the Center for Thrombosis and Hemostasis (Mainz, Germany) and is staff physician at the Clinic of Angiology, University Hospital Zurich, Switzerland. Dr Barco's research interests are in the management of pulmonary embolism and rare thromboembolic disorders. He is involved as Steering Committee member of multinational trials in pulmonary embolism. He is associate editor for Thrombosis Research and Haemostaseologie-Progress in Haemostasis, and serves as a referee for several top journals in the field.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: This is an exemplary case, as such, patient consent is not required.

Conflict of interest: S.B. reports personal fees from Bayer HealthCare, personal fees from BTG Pharmaceuticals, personal fees from LeoPharma, personal fees from Daiichi Sankyo, personal fees from Bayer HealthCare, outside the submitted work.

Funding: This work was not funded. The work of Andrea Gallo, Luca Valerio and Stefano Barco was supported by the German Federal Ministry of Education and Research [BMBF 01EO1003 and 01EO1503].

References

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, *et al.*; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;**41**:543–603.
2. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galie N, *et al.*; Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC) 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;**35**:3033–3069.
3. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M *et al.* Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;**83**:416–420.
4. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. *Arch Intern Med* 2001;**161**:92–97.
5. van der Hulle T, Cheung WY, Kooij S, Beenen LFM, van Bemmel T, van Es J *et al.* Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017;**390**:289–297.
6. Kearon C, de Wit K, Parpia S, Schulman S, Afilalo M, Hirsch A *et al.* Diagnosis of pulmonary embolism with d-dimer adjusted to clinical probability. *N Engl J Med* 2019;**381**:2125–2134.
7. Patel S, Kazerooni EA, Cascade PN. Pulmonary embolism: optimization of small pulmonary artery visualization at multi-detector row CT. *Radiology* 2003;**227**:455–460.
8. van Es J, Douma RA, Schreuder SM, Middeldorp S, Kamphuisen PW, Gerdes VEA *et al.* Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism. *Chest* 2013;**144**:1893–1899.
9. Pruszczyk P, Goliszek S, Lichodziejewska B, Kostrubiec M, Ciurzyński M, Kurnicka K *et al.* Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. *JACC Cardiovasc Imaging* 2014;**7**:553–560.
10. Meinel FG, Nance JW Jr, Schoepf UJ, Hoffmann VS, Thierfelder KM, Costello P *et al.* Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. *Am J Med* 2015;**128**:747–759 e2.
11. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007;**116**:427–433.
12. Henzler T, Roeger S, Meyer M, Schoepf UJ, Nance JW, Jr., Haghi D *et al.* Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. *Eur Respir J* 2012;**39**:919–926.
13. Barco S, Schmidtmann I, Ageno W, Bauersachs RM, Becattini C, Bernardi E *et al.* Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. *Eur Heart J* 2020;**41**:509–518.
14. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J* 2019;**40**:902–910.
15. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J *et al.* Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;**370**:1402–1411.
16. Raschke RA, Gollihare B, Peirce JC. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. *Arch Intern Med* 1996;**156**:1645–1649.
17. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M *et al.* Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;**369**:799–808.

18. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E *et al.* Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;**366**:1287–1297.
19. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003;**362**:523–526.
20. Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V *et al.* Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med* 2010;**170**:1710–1716.
21. Kakkos SK, Kirkilesis GI, Tsolakis IA. Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. *Eur J Vasc Endovasc Surg* 2014;**48**:565–575.
22. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M *et al.* Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;**368**:699–708.
23. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H *et al.* Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med* 2017;**376**:1211–1222.
24. Ende-Verhaar YM, Cannegieter SC, Noordegraaf AV, Delcroix M, Pruszczyk P, Mairuhu ATA *et al.* Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. *Eur Respir J* 2017;**49**:1601792.
25. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;**37**:67–119.
26. Barco S, Russo M, Vicaut E, Becattini C, Bertoletti L, Beyer-Westendorf J *et al.* Incomplete echocardiographic recovery at 6 months predicts long-term sequelae after intermediate-risk pulmonary embolism. A post-hoc analysis of the Pulmonary Embolism Thrombolysis (PEITHO) trial. *Clin Res Cardiol* 2019;**108**:772–778.
27. Held M, Kolb P, Grun M, Jany B, Hubner G, Grgic A *et al.* Functional characterization of patients with chronic thromboembolic disease. *Respiration* 2016;**91**:503–509.