Management of Pulmonary Embolism
The New European Guidelines

Stavros Konstantinides[1,2]
George Chalikias[1]

[1]Department of Cardiology, Democritus
University of Thrace, Greece
[2]Center for Thrombosis and Hemostasis (CTH),
University Medical Center Mainz, Germany

SUMMARY. Acute pulmonary embolism (PE) is the third most frequent acute cardiovascular syndrome, threatening the life of many patients worldwide and imposing a substantial economical burden on health systems. Recent evidence has led to significant progress in the management of the disease and provided a solid basis for the recommendations included in the 2014 update of the European Society of Cardiology Guidelines 2014 (endorsed by the European Respiratory Society). Advanced risk stratification of normotensive patients with 'non-high-risk' PE places an emphasis on clinical prediction rules and assessment of right ventricular function. In PE treatment, recently completed randomised trials using new oral (non-vitamin K-dependent) anticoagulants showed that these agents are at least as effective and probably cause less major bleeding than standard regimens. For intermediate-high-risk PE defined on the basis of imaging tests and laboratory biomarkers, the bleeding risks of full-dose thrombolytic treatment appear too high to justify its use unless clinical signs of haemodynamic decompensation appear. Overall, the new European Guidelines represent a comprehensive, multidisciplinary approach to PE, its acute complications, its management in specific patient populations, and its chronic sequelae such as chronic thromboembolic pulmonary hypertension. They provide a thorough and evidence-based, and at the same time practical and user-friendly guide to physicians involved in the management of PE. *Pneumon 2014, 27(4):294-299.*

Correspondence to:
Stavros V. Konstantinides, MD, FESC
Department of Cardiology
Democritus University of Thrace
University General Hospital
68100 Alexandroupolis, Greece
e-mail: skonst@med.duth.gr

Acute pulmonary embolism (PE), represents a major threat for the health, the well-being and, in severe cases, the life of a large number of patients worldwide. With its acute and long-term complications, it also poses a substantial economical burden on national health systems. In 2014, the results of landmark clinical trials and cohort studies were included in the update of the European Society of Cardiology (ESC) Guidelines on the management of PE[1]. In the 2014 ESC Guidelines, which were endorsed by the European Respiratory Society (ERS), several recommendations regarding

diagnostic strategies and algorithms were confirmed and extended. In parallel, new data extending our knowledge with regard to optimal risk assessment and risk-adapted patient treatment led to major revisions in the recommendations within these areas, and new sections on the long-term sequelae of PE as well as its management in specific patient populations such as pregnant patients and those with active cancer were added (reviewed in[2]). The present article summarises and highlights the most relevant new aspects of the 2014 version as compared with the previous European guidelines published in 2008.

DIAGNOSIS: CLINICAL PREDICTION RULES AND D-DIMER TESTING

Despite the limited sensitivity and specificity of individual symptoms, signs, and common 'baseline' clinical tests, the combination of findings evaluated by clinical judgement or by the use of standardised prediction rules allows us to classify patients with suspected PE into distinct categories of clinical, or pre-test, probability of the disease. Recently, both the Wells and the revised Geneva clinical prediction rule were simplified in order to increase their practicability and adoption into clinical practice[3,4], and the simplified versions were externally validated[5,6]. Whichever rule or version is used, the proportion of patients with confirmed PE can be expected to be approximately 10% in the low-probability category, 30% in the intermediate-probability category, and 65% in the high-clinical probability category when using the three-level classification[7]. If a two-level classification is used, the proportion of patients with confirmed PE in the PE-unlikely category is around 12%[7].

The specificity of a positive D-dimer test in suspected PE decreases steadily with age, to almost 10% in patients >80 years[8]. Using age-adjusted cut-offs may improve the performance of D-dimer testing in the elderly. In a recent meta-analysis, age-adjusted cut-off values (age x 10 μg/L above 50 years) allowed increasing specificity from 34–46% while keeping the sensitivity above 97%[9]. A multicentre, prospective management study evaluated this age-adjusted cut-off level in a cohort of 3346 patients. Patients with a normal age-adjusted D-dimer value did not undergo imaging tests for PE; instead, they were left untreated and followed over a three-month period. On the basis of D-dimer, using the age-adjusted cut-off (instead of the 'standard' 500 μg/L cut-off) increased the number of patients in whom PE could be excluded from 43 (6.4%;

95% CI 4.8–8.5%) to 200 (29.7%; 95% CI 26.4–33.3%), without any additional false-negative findings[10].

SUBSEGMENTAL AND INCIDENTAL PULMONARY EMBOLISM

The clinical significance of isolated subsegmental PE on computed tomographic (CT) pulmonary angiography is controversial. It is likely that a single subsegmental defect does not have the same clinical relevance as multiple, subsegmental thrombi. The positive predictive value is low and inter-observer agreement is poor at this distal level[11]. Compression ultrasound of the leg veins may be helpful in this situation, as the exclusion of proximal deep vein thrombosis in a patient with isolated sub-segmental PE would support a decision against anticoagulation treatment; such cases should be managed on an individual basis, taking into account the clinical probability and the bleeding risk.

The incidental discovery of clinically unsuspected PE on CT is an increasingly frequent problem, arising in 1–2% of all thoracic CT examinations, most often in patients with cancer, but also among those with paroxysmal atrial fibrillation, or heart failure and history of atrial fibrillation[12-14]. No robust data exist to guide the decision on how to manage unsuspected PE, but most experts agree that patients with cancer and those with clots at the lobar or more proximal level should be treated with anticoagulants.

## RISK STRATIFICATION OF PULMONARY EMBOLISM

For prediction of early (in-hospital or 30-day) outcome in patients with acute PE, both the PE-related risk and the patient's clinical status and comorbidities should be taken into consideration. Generally, patients presenting without shock or hypotension, i.e. the vast majority of patients with acute PE, are not at high risk of an adverse early outcome. However, further risk stratification should be considered in these patients after the diagnosis of PE has been confirmed, as this may influence the therapeutic strategy (particularly the need for monitoring and rescue thrombolytic therapy) and possibly the duration of hospitalisation. The 2014 PE Guidelines recommend beginning 'advanced' risk assessment of normotensive patients with confirmed PE with a validated clinical prognostic score, preferably the Pulmonary Embolism Severity Index (PESI)[15]

or its simplified version (sPESI)[16], to distinguish between intermediate and low risk (of an adverse early outcome). Approximately one-third of PE patients are at low risk of an early adverse outcome as indicated by a PESI Class I or II, or an sPESI of 0. On the other hand, patients in PESI Classes III–V have a 30-day mortality rate of up to 24.5%[15], and those with a simplified PESI ≥1 up to 11%[16]. Accordingly, normotensive patients in PESI Class III or higher, or a sPESI of 1 or higher, constitute an intermediate-risk group. Within this category, further risk assessment should be considered, encompassing the status of the right ventricle (RV) to detect PE-induced acute pressure overload and dysfunction. Patients who display evidence of both RV dysfunction (by echocardiography or CT angiography) and elevated cardiac biomarker levels in the circulation (particularly a positive cardiac troponin test indicating myocardial injury) should be classified into an intermediate-high risk category. On the other hand, patients in whom the RV is normal on echocardiography or CT angiography, and/or have normal cardiac biomarker levels, belong to an intermediate-low risk group. The therapeutic implications of this classification are displayed in Figure 1 and discussed below.

TREATMENT AND SECONDARY PROPHYLAXIS WITH NEW ORAL ANTICOAGULANTS

In patients with acute PE, anticoagulation effectively prevents both early death and recurrent symptomatic or fatal VTE. The duration of anticoagulation should cover at least 3 months. Within this period, the 'standard' regimen of acute-phase treatment consists of administering parenteral anticoagulation (unfractionated heparin, low molecular weight heparin, or fondaparinux) over the
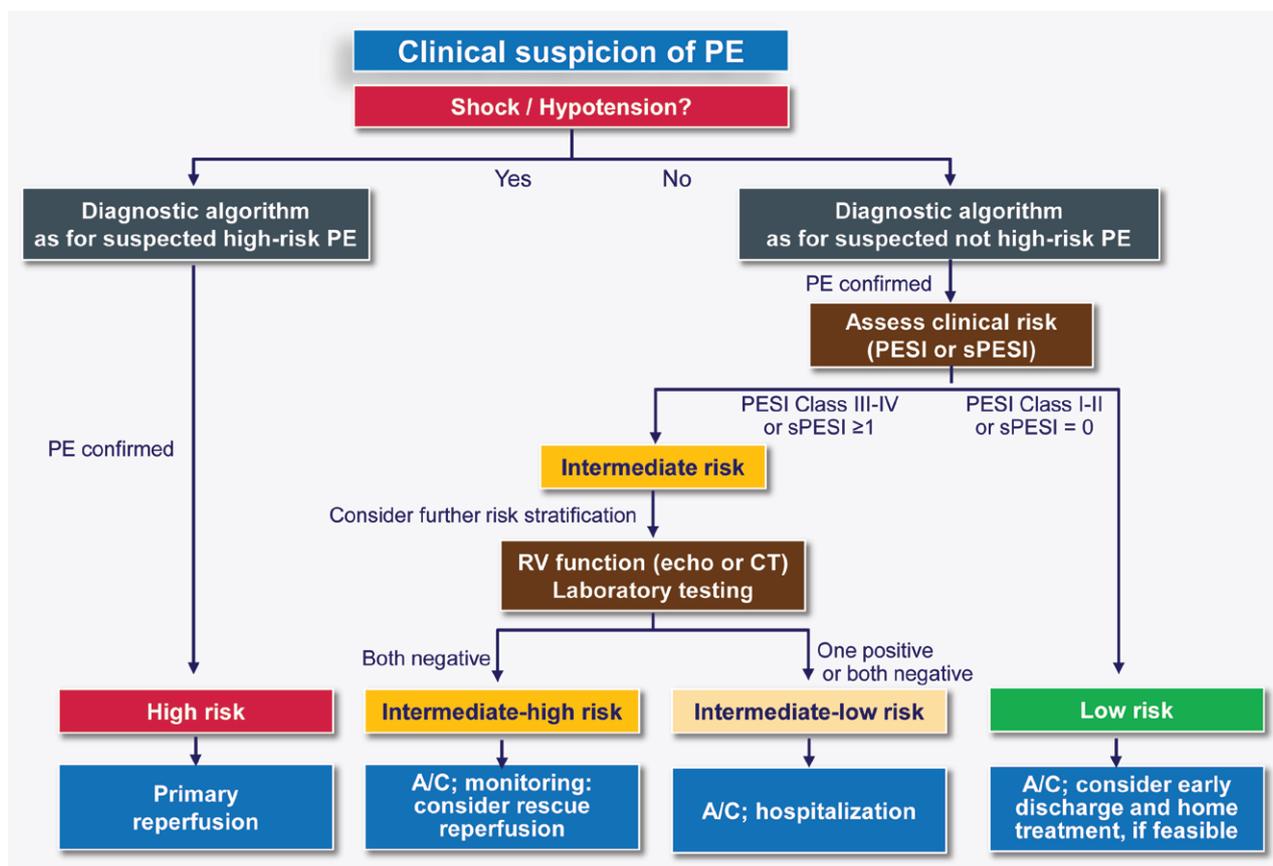
A/C = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = Pulmonary embolism severity index; RV = right ventricular; sPESI = Simplified Pulmonary embolism severity index.

FIGURE 1. Risk-adjusted management strategies in acute PE (adapted from[1]).

first 5–10 days. Parenteral heparin should overlap with the initiation of a vitamin K antagonist. In some cases, extended anticoagulation beyond the first 3 months, or even indefinitely, may be necessary for secondary prevention, after weighing the individual patient's risk of recurrence versus bleeding risk.

The results of the trials using the new, non-vitamin K-dependent oral anticoagulants (NOACs) dabigatran[17,18], rivaroxaban[19,20], apixaban[21] or edoxaban[22] in the treatment of VTE indicated, both individually and in a meta-analysis[23], that these agents are non-inferior (in terms of efficacy) and possibly safer (particularly in terms of major bleeding) than the standard heparin/VKA regimen. As a result, NOACs are recommended in the 2014 PE Guidelines as an alternative to standard treatment. Currently, rivaroxaban, dabigatran and apixaban are approved for treatment of VTE in the European Union; edoxaban is under regulatory review. Experience with NOACs in clinical practice is accumulating at an increasing pace.

Three NOACs, dabigatran[24], rivaroxaban[20], and apixaban[25], have also been evaluated in the extended treatment of patients with VTE. To be included in the extended studies, patients needed to have completed the initial and long-term anticoagulation phase. Taken together, the results of the trials using NOACs in the extended treatment of VTE are in line with those of the studies that tested these agents in the acute-phase treatment and standard duration of anticoagulation after PE or VTE. They indicate that NOACs are both effective (in terms of prevention of symptomatic or fatal recurrence of VTE) and safe (particularly in terms of major bleeding), probably safer than standard VKA regimens. Accordingly, the 2014 PE Guidelines recommend that treatment with a NOAC should be considered as an alternative to the use of a vitamin K antagonist if extended secondary prophylaxis is deemed necessary.

REPERFUSION TREATMENT FOR INTERMEDIATE-RISK PULMONARY EMBOLISM

As already mentioned, an echocardiogram or CT scan indicating RV dysfunction in combination with a positive cardiac troponin test classifies a normotensive patient with PE into an intermediate-high-risk group. In a large multicentre investigator-initiated European trial, full-dose systemic thrombolytic therapy effectively prevented potentially life-threatening haemodynamic decompensation or collapse in these patients, but this benefit was counterbalanced by a high risk of haemorrhagic stroke or

major non-intracranial bleeding[26]. Accordingly, systemic thrombolysis is not routinely recommended as primary treatment for patients with intermediate-high-risk PE; instead, these patients should be monitored for approximately 48-72 hours and rescue thrombolysis should be considered if clinical signs of haemodynamic decompensation appear. Surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative rescue procedures for patients with intermediate-high-risk PE, in whom haemodynamic decompensation appears imminent and the anticipated bleeding risk under systemic thrombolysis is high[27].

EARLY DISCHARGE AND HOME (OUTPATIENT) TREATMENT OF CAREFULLY SELECTED PATIENTS

Recent multicentre clinical trials investigated the three-month clinical outcome of patients with PE who were discharged early or treated entirely as outpatients. Overall, the proportion of screened patients who were identified as eligible for home treatment varied widely, ranging from 13 to 51%[28]. In a meta-analysis of 14 (mostly small) studies, the pooled incidence rates of recurrent VTE, major bleeding and total mortality did not differ significantly between outpatients, patients discharged early, and those treated as inpatients[29]. Based on the encouraging available data, low-risk patients in the PESI Class I or II, and probably those with sPESI of 0, should be considered for early discharge and outpatient treatment, if this appears feasible based on the patient's anticipated compliance as well as his/her family and social background. Further management trials are necessary to better define the criteria that will permit early discharge and home treatment of low-risk patients with acute PE.

A NEW, RISK-ADAPTED MANAGEMENT ALGORITHM FOR PULMONARY EMBOLISM

A risk-adapted management algorithm for acute PE, as proposed in the 2014 PE Guidelines, is shown in Figure 1.

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a debilitating disease caused by chronic obstruction of major pulmonary arteries. CTEPH is assumed

to be a long-term complication of PE, with a reported cumulative incidence of 0.1–9.1% within the first two years after a symptomatic PE event[30].

The 2014 PE Guidelines specify that CTEPH should be ruled out in PE survivors with persistent dyspnoea, but routine screening for CTEPH in asymptomatic survivors of PE is currently not recommended. In all patients with diagnosed CTEPH, the assessment of operability and decisions regarding other treatment strategies should be made by a multidisciplinary team of experts. Life-long anticoagulation is recommended in all patients with CTEPH, and surgical pulmonary endarterectomy (PEA) should be performed in those patients who are considered operable by a CTEPH team including at least one experienced PEA surgeon. Medical treatment with the recently approved agent riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment, or those with inoperable disease as judged by an expert CTEPH team (see above). An emerging interventional treatment option for 'inoperable' patients – percutaneous balloon pulmonary angioplasty – is also mentioned in the updated CTEPH management algorithm but it is not yet formally recommended.

PULMONARY EMBOLISM IN SPECIFIC PATIENT POPULATIONS

The 2014 PE Guidelines emphasize that suspicion of PE in pregnancy warrants formal diagnostic assessment with validated methods, exactly as suspected in non-pregnant patients. Venous compression ultrasonography may be considered in order to avoid unnecessary irradiation, as a diagnosis of proximal deep vein thrombosis confirms PE. Perfusion scintigraphy, which exposes the mother's breast to lower radiation doses compared to CT angiography, may be deemed to rule out suspected PE in pregnant women with normal chest X-ray. A weight-adjusted dose of low molecular weight heparin (not fondaparinux) is the recommended therapy during pregnancy in patients without shock or hypotension. Importantly, NOACs are contraindicated in pregnant patients.

The overall risk of venous thromboembolism in patients with cancer is four times as great as in the general population[31]. Although the largest absolute numbers of VTE episodes occur in patients with lung, colon, and prostate cancer, the relative risk for VTE is highest in multiple myeloma, brain, and pancreatic cancer (46-, 20-,

and 16-fold increased vs. healthy controls, respectively)[32]. Patients receiving chemotherapy have a six-fold increase in the adjusted risk ratio for VTE compared with a healthy population[31]. Nevertheless, prophylactic anticoagulation is not routinely recommended during ambulatory anti-cancer chemotherapy, with the exception of thalidomide- or lenalidomide-based regimens in multiple myeloma[33,34]. The risk of VTE increases over 90-fold in the first 6 weeks after cancer surgery, compared with that in healthy controls, and is second only to the risk of VTE after hip or knee replacement surgery. For patients with PE and cancer, weight-adjusted subcutaneous low molecular weight heparin should be considered for the first 3–6 months; evidence with new oral anticoagulants is still limited in this early time period. For patients with PE and cancer, extended -oral or parenteral- anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period, or until the cancer is cured.

CONCLUSIONS

Considerable progress in the diagnosis, treatment and secondary prevention of venous thromboembolism could be made in the past few years, and management concepts continue to evolve at a rapid pace. Thanks to the joint efforts of experts nominated by the ESC and the ERS in close collaboration, the new (2014) European Pulmonary Embolism Guidelines represent a contemporary multidisciplinary approach to acute PE. The Guidelines Task Force took every effort to issue impartial, evidence-based recommendations, while at the same time providing a practical guide to physicians being involved in the management of pulmonary embolism.

REFERENCES

1. Konstantinides S, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC)Endorsed by the European Respiratory Society (ERS). Eur Heart J 2014;35:3033-73.
2. Konstantinides SV, Torbicki A. Management of pulmonary embolism: recent evidence and the new European guidelines. Eur Respir J 2014;44:1385-90.
3. Gibson NS, Sohne M, Kruip MJ, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thromb Haemost 2008;99:229-34.
4. Klok FA, Mos IC, Nijkeuter M, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary

embolism. Arch Intern Med 2008;168:2131-6.

5. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med 2011;154:709-18.

6. Douma RA, Gibson NS, Gerdes VE, et al. Validity and clinical utility of the simplified Wells rule for assessing clinical probability for the exclusion of pulmonary embolism. Thromb Haemost 2009;101:197-200.

7. Ceriani E, Combescure C, Le Gal G, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost 2010;8:957-70.

8. Righini M, Goehring C, Bounameaux H, Perrier A. Effects of age on the performance of common diagnostic tests for pulmonary embolism. Am J Med 2000;109:357-61.

9. Schouten HJ, Geersing GJ, Koek HL, et al. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. BMJ 2013;346:f2492.

10. Righini M, Van EJ, den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117-24.

11. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. Clin Appl Thromb Hemost 2012;18:20-6.

12. Jia CF, Li YX, Yang ZQ, Zhang ZH, Sun XX, Wang ZQ. Prospective evaluation of unsuspected pulmonary embolism on coronary computed tomographic angiography. J Comput Assist Tomogr 2012;36:187-90.

13. Palla A, Rossi G, Falaschi F, Marconi L, Pistolesi M, Prandoni P. Is incidentally detected pulmonary embolism in cancer patients less severe? A case-control study. Cancer Invest 2012;30:131-4.

14. Sahut DM, Caumont PA, Planquette B, et al. Risk factors and clinical outcome of unsuspected pulmonary embolism in cancer patients: a case-control study. J Thromb Haemost 2012;10:2032-2038.

15. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172:1041-46.

16. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9.

17. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014;129:764-72.

18. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342-52.

19. Buller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.

20. Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.

21. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.

22. Buller HR, Decousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013;369:1406-15.

23. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12:320-8.

24. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:709-18.

25. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.

26. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 2014;370:1402-11.

27. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129:479-86.

28. Lankeit M, Konstantinides S. Is it time for home treatment of pulmonary embolism? Eur Respir J 2012;40:742-9.

29. Zondag W, Kooiman J, Klok FA, Dekkers OM, Huisman MV. Outpatient versus inpatient treatment in patients with pulmonary embolism: a meta-analysis. Eur Respir J 2013;42:134-44.

30. Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 2013;41:462-8.

31. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, III. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000;160:809-15.

32. Cronin-Fenton DP, Sondergaard F, Pedersen LA, et al. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. Br J Cancer 2010;103:947-53.

33. Akl EA, Vasireddi SR, Gunukula S, et al. Anticoagulation for patients with cancer and central venous catheters. Cochrane Database Syst Rev 2011;(4):CD006468.

34. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. J Clin Oncol 2011;29:986-93.