

Editorial Focus

Recurrent venous thromboembolism: Quite harmless after all?

Stavros V. Konstantinides

Department of Cardiology and Pulmonary Medicine, Georg August University of Goettingen, Goettingen, Germany

Acute pulmonary embolism (PE) and deep venous thrombosis (DVT) are pathophysiologically linked manifestations of the same disease, but their natural course, prognosis, and therapeutic management are quite different in clinical practice. Clearly, the risk of death related to the initial acute episode is higher in patients who present with PE than in those with DVT (1). Overall, acute symptomatic PE, which typically occurs 3–7 days after the onset of DVT, has been reported to be associated with a case fatality rate ranging from 7% to 11%, or even higher, in the acute phase (2, 3). Mortality rates are particularly high in the small proportion (approximately 5%) of patients who have clinically massive PE, i.e. those who are in cardiogenic shock on admission. On the other hand, prognostically unfavourable signs of right ventricular dysfunction and myocardial injury may be detected on echocardiography or computed tomography scan, or by biomarker testing, in as many as 50% of all patients with PE, including many of those who are normotensive at presentation.

Immediate institution of heparin anticoagulation, while awaiting definite confirmation, is life-saving in acute PE and clearly recommended in current guidelines (4–6), as less than 10% of all deaths related to the acute episode have been shown to occur in adequately anticoagulated patients (7). In addition to heparin, patients with clinically massive PE and selected normotensive patients with right ventricular dysfunction might benefit from medical (i.e. thrombolysis) or surgical recanalisation treatment (8, 9).

PE and particularly idiopathic, unprovoked PE is, like DVT, a life-long disease, and chronic secondary prophylaxis with oral anticoagulants is necessary. In fact, without continuing anticoagulation, as many as 50% of patients with symptomatic proximal DVT or PE will suffer a recurrent episode within the first three months (7). The frequency of recurrence appears to be independent of the initial clinical manifestation of venous thromboembolism, i.e. whether the patient suffered DVT or PE, but nevertheless venous thromboembolism is almost three times more likely to recur as PE if also the initial event was PE than if it was DVT (1). This observation renders effective secondary

prophylaxis in patients who have suffered PE a particularly relevant issue.

The optimal duration of oral anticoagulation after an initial episode of idiopathic or unprovoked PE has been extensively reviewed in recent guidelines (4) but still continues to be poorly standardised and partly controversial. As a result, decisions are often made based on the clinicians' individual judgement. In their most recent study which appears in the current issue of *Thrombosis and Haemostasis*, White et al. begin by elegantly summarising the most important clinical factors which should be considered in the decision on how long to anticoagulate: (a) The risk of recurrent venous thromboembolism for the patient if anticoagulation is stopped, (b) the risk of bleeding if therapy is continued; and, most importantly perhaps, (c) the risk of death or serious morbidity if the patient suffers recurrent PE. With their retrospective registry, the authors attempted to bring more light into the above issues and particularly into the case-fatality rates of recurrent PE.

Most of the studies addressing recurrence prophylaxis for venous thromboembolism have included patients with DVT rather than focussing on PE alone. From the available data, it appears that the overall long-term recurrence rates may be 30% or even higher after 8–10 years (10–12), and it was suggested that indefinite treatment is capable of reducing the risk for recurrent thromboembolism by up to 90% (13). On the other hand, and importantly, studies and meta-analyses have also shown that the benefits of oral anticoagulation are partly offset by the increased risk of major bleeding (13, 14). Notably, vitamin K antagonists are highly effective in preventing recurrent thromboembolism during treatment, but they do not eliminate the risk of subsequent recurrence after their discontinuation regardless of the duration of treatment (15, 16).

In the present study published in *Thrombosis and Haemostasis*, White et al. (17) retrospectively review the hospital records and discharge data of 3,456 patients below 55 years of age after an initial episode of symptomatic PE. Recurrence and death rates were determined over a mean period of 3.2 years. Overall, 12% of patients suffered from recurrent venous thromboembolism during this period, yielding a recurrence rate of 13% during the

Correspondence to:
Stavros V. Konstantinides, MD
Department of Cardiology and Pulmonary Medicine
Georg August University of Goettingen
D-37099 Goettingen, Germany
Tel.: +49 551 39 8927.
Fax: +49 551 39 14131
E-mail: skonstan@med.uni-goettingen.de
<http://www.herzzentrum-goettingen.de>

Received March 7, 2008
Accepted March 7, 2008

Prepublished online March 12, 2008
doi:10.1160/TH08-03-0137

first six months after the index event and 2.9% per year from six months to five years. These figures are lower than those in previous publications but not really surprising. The sensational news, however, was the extremely low case-fatality rate of 0.16% per year starting at six months after the index event. Interestingly, these data appear to agree with the annual rate of definite PE-related deaths after discontinuation of anticoagulation (0.19%) recently reported by Douketis et al. in an inception cohort derived from two studies (15).

Can the results of the two studies be interpreted as indicating that recurrent idiopathic PE is a harmless event? Do they suffice to support the hypothesis that six months of oral anticoagulation are adequate for most patients, particularly for the younger ones? The registry performed by White et al. included a large number of patients and was carefully conducted. In particular, care was taken to exclude patients with provoking risk factors (except for thrombophilic disorders and, apparently, oral contraceptive use or hormonal replacement therapy) and independently adjudicate the cause of death wherever possible. On the other hand, the reader is left with the impression that the authors somehow focussed on a very low-risk population of patients with PE. In particular, a 28-day fatality rate of 1.5% and a six-month fatality rate of 1.7% was reported. This is definitely much lower compared to the fatality rates in large prospective registries which included unselected patients with acute PE (2). The possibility exists that PE may have been missed as the cause of death in a number of severe cases in the records studied, and this may also

have been true for recurrent events. Moreover, and perhaps most important of all, we can only speculate on how many of these patients were on oral anticoagulation or had discontinued therapy when they suffered venous thromboembolism. Without this critical piece of information, the findings of the study cannot be used to elaborate the optimal duration of anticoagulation after an initial event of acute PE.

Current guidelines recommend that patients with an initial episode of unprovoked PE be treated with vitamin K antagonists for at least three months. Patients should then be evaluated on an individual basis for the risks versus benefits of treatment continuation. Indefinite anticoagulant therapy is to be considered for patients with a first unprovoked event of proximal DVT or PE and a low risk of bleeding, particularly when this is consistent with the patient's wish and preference. The findings of the study by White et al. may be used as an argument to "support" the decision of physicians and patients who choose to discontinue treatment, but they cannot be generalized to all patients with PE. Further work will be necessary in order to determine whether, and to what extent, the severity of the initial event and possibly other clinical and haemodynamic factors, such as persistent pulmonary hypertension on echocardiography, determine recurrence-related fatality rates. It also remains to be confirmed whether D-dimer testing one month after discontinuation of vitamin K antagonists may be used to resume or definitely terminate therapy in patients who have received oral anticoagulants for three months after the first episode of idiopathic DVT or PE.

References

1. Murin S, Romano PS, White RH. Comparison of outcomes after hospitalization for deep venous thrombosis or pulmonary embolism. *Thromb Haemost* 2002; 88: 407–414.
2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999; 353: 1386–1389.
3. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. *J Am Coll Cardiol* 1997; 30: 1165–1171.
4. Buller HR, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126: 401S–428S.
5. British Thoracic Society. Guidelines for the management of suspected acute pulmonary embolism. *Thorax* 2003; 58: 470–483.
6. European Society of Cardiology TFoPE. Guidelines on diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2000; 21: 1301–1336.
7. Kearon C. Natural history of venous thromboembolism. *Circulation* 2003; 107: 122–130.
8. Leacche M, Unic D, Goldhaber SZ, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg* 2005; 129: 1018–1023.
9. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002; 347: 1143–1150.
10. Hansson PO, Sorbo J, Eriksson H. Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. *Arch Intern Med* 2000; 160: 769–774.
11. Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. *Arch Intern Med* 2000; 160: 761–768.
12. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996; 125: 1–7.
13. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism [published erratum in *N Engl J Med* 1999; 341:298]. *N Engl J Med* 1999; 340: 901–907.
14. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003; 139: 893–900.
15. Douketis JD, Gu CS, Schulman S, et al. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. *Ann Intern Med* 2007; 147: 766–774.
16. Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003; 139: 19–25.
17. White R, Zhou H, Murin S. Death due to recurrent thromboembolism among younger healthier individuals hospitalized for idiopathic pulmonary embolism. *Thromb Haemost* 2008; 99: 683–690.