

## Editorial Focus

# Are we ready to start outpatient treatment for pulmonary embolism?

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Ten years ago, most patients suffering from pulmonary embolism (PE) were given intravenous heparin and were confined to bed for several days, even if the disease was clinically stable. The advent of subcutaneous treatment with low-molecular-weight heparins (LMWH) and less intensive monitoring made it possible for patients to become mobile again much sooner, with the exception of the small number of patients that were clinically unstable and required oxygen or haemodynamic support. Not surprisingly, some patients then asked their doctors why they needed to be hospitalised for such simple treatment and requested early discharge. Large, randomised, controlled trials have demonstrated that the outpatient treatment of deep-vein thrombosis (DVT) with LMWH is as safe as hospital-based treatment with intravenous unfractionated heparin (UFH) (1). As PE and DVT are considered to be different manifestations of the same disease, these findings suggested that patients with PE could also benefit from early discharge. The length of hospital stay for patients with PE has thus been considerably reduced at some institutions, and several case series of PE patients treated entirely on an outpatient basis have been reported, with results comparing favourably with inpatient care, as indicated by Janjua et al. in this issue of *Thrombosis and Haemostasis* (2). In the large Matisse PE study, 14% of the patients receiving subcutaneous fondaparinux were at least partly treated at home (3). However, the risk of death in general is higher for PE than for DVT, and additional evidence is required before the results of outpatient treatment for DVT can be extrapolated to PE.

So, what do we need to expand the use of home treatment for PE? We first need to select the patients with a low risk of major complications during the initiation phase of anticoagulant treatment. Second, we need robust data concerning the outcome of patients treated as outpatients. Third, we ideally require controlled clinical trials comparing the hospital-based and ambulatory treatment of PE, demonstrating that ambulatory care is at least as safe as hospital-based care. Finally, we need to set up rules and procedures in each institution to provide these patients with the same degree of safety as in hospital-based trials.

The systematic review of outpatient treatment for PE reported by Janjua et al. (2) provides us with the results of seven case series (6 prospective and 1 retrospective) reporting on a total of 593 patients treated either entirely at home or after a short hospital stay. All patients were described as low-risk patients or patients with small or medium-sized PE; unstable patients were explicitly excluded from the studies. The frequency of recurrent venous thromboembolism was reported to vary between 1% and 6.2% and that of major bleeding varied between 0% and 2.7% after one to six months of follow-up. In this low-risk population, home-based treatment gave promising results, with event rates approaching those reported with conventional hospital-based treatment.

Are these data convincing enough to change the initial treatment of PE patients? Several limitations should temper our enthusiasm. First, these studies include a limited total number of patients, and the confidence intervals remain large, the upper limit of the 95% confidence interval for recurrent PE varying from 5.4% to 18.2%. Second, although most studies were prospective, and recurrent events were objectively confirmed in all cases, the criteria for objective confirmation were not given in two studies. More importantly, due to the study design, recurrent events and major bleeding (not prospectively defined in all studies) were not assessed as blinded to treatment. Third, in most of these case series, the study population was not precisely defined, limiting reproducibility in everyday practice.

To date, the randomisation of patients with acute PE to hospital- versus home-treatment groups has not been considered in any published trial. Two recent randomised trials included patients with acute PE who were treated as outpatients. The first, which compared two LMWH preparations for the outpatient treatment of acute venous thromboembolism, included 90 patients with acute PE. Two of these patients had recurrent venous thromboembolism, but the study included no control group of PE patients treated as inpatients (4). The second, which compared subcutaneous fixed-dose UFH and LMWH in patients with acute venous thromboembolism, included 52 patients with

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acute PE treated entirely as outpatients, but these patients were not analysed separately (5). One randomised, controlled trial, the Safety Study of Outpatient Treatment for Pulmonary Embolism (OTPE) NCT00425542, is currently evaluating the safety of outpatient treatment for PE with a randomised design. The study is recruiting 300 outpatients with PE diagnosed in the emergency departments of the participating institutions. These patients are randomised to groups treated with enoxaparin and warfarin either at hospital or on an outpatient basis. The results of this trial will probably increase the evidence in favour of treating a substantial proportion of PE patients with LMWH at home.

Clinical prediction rules have been developed for selecting the patients with acute PE most suitable for treatment out of hospital. The PESI index, developed by Aujeski et al., has been validated in several different series of patients with PE (6, 7). The prediction rule is based entirely on clinical variables and makes it possible to select five groups of patients with different mortality rates. Patients in the two lowest risk groups have mortality rates below 2% and are currently included in the OPTPE trial.

What about echocardiography and cardiac biomarkers? A number of studies have suggested that right ventricular enlargement on echocardiography or spiral computed tomography or right ventricular dysfunction, as detected by high plasma con-

centrations of cardiac biomarkers, such as troponin, brain natriuretic peptide or pro-brain natriuretic peptide, are associated with a higher risk of adverse events in hospital or of early death in patients with PE. The positive predictive value of such findings remains low, but the absence of right ventricular enlargement or dysfunction seems to be associated with a very low risk of adverse outcome. However, most of the studies of these aspects have been single-centre studies, and the results were generally not adjusted for established clinical signs of poor outcome (8). Large, prospective multicentre studies are required to confirm that echocardiography, spiral computed tomography and biomarkers provide significant additional prognostic information over and above that obtained through clinical observation in patients with PE.

The period of overlap in anticoagulation between heparin, LMWH or fondaparinux and vitamin K antagonists is traditionally referred to as the "initial treatment" and patients are usually discharged from hospital at the end of this period. However, new orally administered anticoagulant drugs make it possible to treat patients with PE without the need for initial parenteral treatment may modify this pattern of treatment in the future by eliminating the boundaries between initial treatment and secondary prophylaxis of venous thromboembolism.

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