

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/20073> holds various files of this Leiden University dissertation.

**Author:** Zondag, Wendy

**Title:** Pulmonary embolism : outpatient treatment and risk stratification

**Date:** 2012-11-01



# **Chapter 1**

**General introduction**



For more than 100 years it has been recognized that pulmonary embolism (PE), a condition caused by the formation of a thrombus in the pulmonary arteries, could lead to severe dyspnea.<sup>1</sup> However, no effective treatment was available until the first part of the 20th century and the majority of the patients with PE died.<sup>2</sup>

It was not until 1938 that the first claims of successful anticoagulant treatment with heparin were published.<sup>3,4</sup> However, there was one disadvantage of the use of heparin: it had to be administered intravenously. Because of the intravenous administration, PE patients had to stay in the hospital and therefore could only be treated for a short period of time. A discovery by two veterinarians in 1920 was the start for the development of the first anticoagulant for long term treatment. They observed that cattle that had eaten spoiled hay suffered from massive hemorrhage.<sup>5</sup> This led to the discovery of a substance from the sweet clover, named coumarin, which was responsible for the anticoagulant mechanism that caused the bleeding in the cattle. Coumarin was extracted in the laboratory for medicinal use to prevent further thrombus formation in patients with PE. Because coumarin was administered orally, from this point in time patients could be treated out of the hospital and the duration of anticoagulant treatment could be prolonged.

Another breakthrough came in 1960, when the first clinical trial investigating the use of heparin combined with coumarin was published.<sup>2</sup> This trial demonstrated that the prognosis of patients with PE improved largely upon treatment with the combination of intravenous unfractionated heparin and coumarin. Afterwards, the treatment of PE patients with the combination of heparin and coumarin was considered standard patient care for many decades.<sup>3</sup>

The next large change in anticoagulant management came with the introduction of low-molecular weight heparin (LMWH), which could be administered subcutaneously and was at least as effective as unfractionated heparin administered intravenously.<sup>6</sup> Because unfractionated heparin had to be administered intravenously, patients who were diagnosed with PE were admitted to the hospital for at least five days. After the introduction of LMWH, the duration of hospital admission shortened over the years.<sup>7</sup> In the last decade small observational studies have been published, which gave a first indication towards the safety and efficacy of the outpatient treatment of PE patients.<sup>8-10</sup> The first systematic review on outpatient treatment of PE patients indicated that the quality of those observational studies was too low to incorporate outpatient treatment of patients with PE in standard patient care.<sup>11</sup>

Over the last years, more solid evidence on the safety of outpatient treatment in PE patients is accumulating.<sup>12</sup> In the first part of this thesis more recent publications on outpatient treatment of patients with PE are extensively discussed. The results of the Hestia study, a prospective multicenter cohort study on outpatient treatment of PE patients, which we performed in conjunction with 12 hospitals in The Netherlands, are presented in chapter 2 and 3. In chapter 4, the results of all available studies on outpatient treatment of PE patients in the literature are summarized in a meta-analysis.

The second aim of this thesis was to compare methods for risk stratification, which discriminate low from high risk PE patients, in order to treat the low risk patients at home safely.<sup>13</sup> Several methods for risk stratification are available<sup>14</sup>: methods based on clinical signs and symptoms<sup>15,16</sup>, laboratory values<sup>17,18</sup> or imaging modalities<sup>19,20</sup>. In the Hestia study, described in chapter 2, the Hestia criteria were used to select low risk PE patients for outpatient treatment. The Hestia criteria were compared to two other methods for risk stratification, the Pulmonary Embolism Severity Index (PESI) and the assessment of right ventricular dysfunction on computed tomography and the results of these analyses are found in chapters 5 and 6. Chapter 7 describes the potential role of repeated measurements of the laboratory value NT-proBNP in selecting patients with PE for outpatient treatment or early discharge. Finally, in chapters 8 and 9 the prognosis of patients with PE and different baseline characteristics is described: patients with provoked PE versus unprovoked PE and patients presenting to a university hospital versus patients in a non-university hospital.

## References

1. Virchow R. *Cellular Pathology 1863*. Dover, New York; 1971.
2. BARRITT DW, JORDAN SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* 1960; 1:1309-1312.
3. Dalen JE. Pulmonary embolism: what have we learned since Virchow?: treatment and prevention. *Chest* 2002; 122:1801-1817.
4. Murray D, Best C. Heparin and thrombosis. *JAMA* 1938; 110:118-119.
5. LINK KP. The discovery of dicumarol and its sequels. *Circulation* 1959; 19:97-107.
6. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 2004; 140:175-183.
7. Aujesky D, Stone RA, Kim S, Crick EJ, Fine MJ. Length of hospital stay and postdischarge mortality in patients with pulmonary embolism: a statewide perspective. *Arch Intern Med* 2008; 168:706-712.
8. Beer JH, Burger M, Gretener S, Bernard-Bagattini S, Bounameaux H. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. *J Thromb Haemost* 2003; 1:186-187.
9. Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS. Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* 2000; 83:209-211.
10. Siragusa S, Arcara C, Malato A, Anastasio R, Valerio MR, Fulfaro F, et al. Home therapy for deep vein thrombosis and pulmonary embolism in cancer patients. *Ann Oncol* 2005; 16 Suppl 4:iv136-iv139.
11. Janjua M, Badshah A, Matta F, Danescu LG, Yaekoub AY, Stein PD. Treatment of acute pulmonary embolism as outpatients or following early discharge. A systematic review. *Thromb Haemost* 2008; 100:756-761.
12. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic Therapy for VTE Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141:e419S-e494S.
13. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk P, et al. 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). *Eur Heart J* 2008; 29:2276-2315.
14. Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med* 2010; 363:266-274.
15. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005; 172:1041-1046.
16. Wicki J, Perrier A, Perneger TV, Bounameaux H, Junod AF. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. *Thromb Haemost* 2000; 84:548-552.

17. Jimenez D, Uresandi F, Otero R, Lobo JL, Monreal M, Marti D, et al. Troponin-based risk stratification of patients with acute nonmassive pulmonary embolism: systematic review and metaanalysis. *Chest* 2009; 136:974-982.
18. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. *Am J Respir Crit Care Med* 2008; 178:425-430.
19. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation* 2000; 101:2817-2822.
20. van der Meer RW, Pattynama PM, van Strijen MJ, van den Berg-Huijsmans AA, Hartmann IJ, Putter H, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. *Radiology* 2005; 235:798-803.