Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study


*Section of Vascular Medicine, Department of General Internal Medicine-Endocrinology, LUMC, Leiden; †Department of General Internal Medicine, Haga Hospital, The Hague; ‡Department of Pulmonology, Spaarne Hospital, Hoofddorp; §Department of Epidemiology, LUMC; **Department of Pulmonology, Diaconessenhuis, Leiden; ‡‡Department of Pulmonology, Medical Spectrum Twente, Enschede; ††Department of General Internal Medicine, Rode Kruis Hospital, Beverwijk; ‡‡‡Department of Internal Medicine, VU University Medical Center, Amsterdam; §§Department of General Internal Medicine, Rijnstate Hospital, Arnhem; ****Department of General Internal Medicine, Rijnland Hospital, Leiderdorp; *****Department of Pulmonology, LUMC, Leiden; ††††Department of Hematology, Erasmus Medical Center, Rotterdam; ‡‡‡‡Department of General Internal Medicine, Bronovo Hospital, The Hague; and §§§Department of General Internal Medicine, Haaglanden Medical Center, The Hague, the Netherlands


Summary. Background: Traditionally, patients with pulmonary embolism (PE) are initially treated in the hospital with low molecular weight heparin (LMWH). The results of a few small non-randomized studies suggest that, in selected patients with proven PE, outpatient treatment is potentially feasible and safe. Objective: To evaluate the efficacy and safety of outpatient treatment according to predefined criteria in patients with acute PE. Patients and Methods: A prospective cohort study of patients with objectively proven acute PE was conducted in 12 hospitals in The Netherlands between 2008 and 2010. Patients with acute PE were triaged with the predefined criteria for eligibility for outpatient treatment, with LMWH (nadroparin) followed by vitamin K antagonists. All patients eligible for outpatient treatment were sent home either immediately or within 24 h after PE was objectively diagnosed. Outpatient treatment was evaluated with respect to recurrent venous thromboembolism (VTE), including PE or deep vein thrombosis (DVT), major hemorrhage and total mortality during 3 months of follow-up. Results: Of 297 included patients, who all completed the follow-up, six (2.0%; 95% confidence interval [CI] 0.8–4.3) had recurrent VTE (five PE [1.7%] and one DVT [0.3%]). Three patients (1.0%, 95% CI 0.2–2.9) died during the 3 months of follow-up, none of fatal PE. Two patients had a major bleeding event, one of which was fatal intracranial bleeding (0.7%, 95% CI 0.08–2.4). Conclusion: Patients with PE selected for outpatient treatment with predefined criteria can be treated with anticoagulants on an outpatient basis. (Dutch Trial Register No 1319; http://www.trialregister.nl/trialreg/index.asp).

Keywords: home treatment, outpatient treatment, pulmonary embolism, venous thromboembolism.

Introduction

Pulmonary embolism (PE) is a common condition with a variable clinical presentation, ranging from patients with minor thoracic pain to patients with fatal PE [1]. The risk of mortality and other serious events differs. Patients presenting with symptoms of shock have a high risk of short-term mortality of approximately 30% [2–4], whereas patients who maintain a normal blood pressure have a risk of PE-attributable mortality of 2–6% [2–4]. Patients with a risk of short-term mortality of < 1% are typically considered to be low-risk patients [4], and these patients may potentially be amenable to outpatient treatment.

In patients with deep vein thrombosis (DVT), outpatient treatment with low molecular weight heparin (LMWH) followed by vitamin K antagonists (VKAs) is commonly accepted [5,6]. As these patients have a low risk of developing (fatal) PE, outpatient treatment of patients with DVT has become the worldwide standard of care [7].

In the last decade, several small observational studies on outpatient treatment in PE have been published [8–21]. These
studies on outpatient treatment include nine prospective and five retrospective studies, with the largest prospective study containing 152 patients entirely treated at home. The majority of the prospective studies used simple bedside criteria for selection of patients for outpatient treatment [9,10,12,19–21]. In these studies, no PE-related mortality occurred, only one patient died of major bleeding, and non-fatal recurrence rates of venous thromboembolism (VTE) varied from 0% to 6.2% [22].

The objective of the Hestia Study was to confirm the results of these small cohort studies in a large study, and provide proof that the incidences of VTE recurrence, major bleeding and mortality are very low in patients selected with a simple set of exclusion criteria.

Materials and methods

Design overview

The Hestia Study was a multicenter prospective cohort study in patients with acute PE who were selected for outpatient treatment if they did not meet a predefined set of exclusion criteria. We evaluated the efficacy and safety of outpatient anticoagulant treatment with LMWH followed by VKAs for at least 3 months. The protocol was approved by the institutional review board of each participating hospital. The data were collected and stored in the database by the investigators. All suspected outcome events were classified by an independent central adjudication committee, whose members were not participating in the study. It was established that an independent data and safety monitoring board would periodically review the studies’ outcomes after every 50 included patients and advise the investigators. The manuscript was written by the investigators, and they vouch for the accuracy and completeness of the reported data.

Setting and participants

Patients were recruited from 12 hospitals in The Netherlands (three academic and nine non-academic hospitals). Consecutive patients, meeting the following inclusion criteria, were potentially eligible: over 18 years of age with objectively proven acute PE, defined as duration of symptoms lasting for longer than 14 days and no acute worsening within the last 14 days, were not included. Patients were triaged according to predefined exclusion criteria (Table 1). This checklist with 11 items can be used as a bedside test and can be completed within 5 min. Patients could not be treated at home if one of the exclusion criteria (Table 1) was met; otherwise, patients were eligible for outpatient treatment.

For study reasons, additional exclusion criteria were as follows: impossibility of achieving the required 3-month follow-up (e.g. no fixed address, or foreign citizen) or life-expectancy < 3 months. After giving written informed consent and starting treatment with LMWH, patients were sent home either immediately, or within 24 h after the diagnosis of PE for outpatient treatment.

Interventions

Patients were treated with standard anticoagulant therapy according to international guidelines [7]. Initial treatment consisted of once-daily subcutaneous LMWH (nadroparin) corrected for body weight (11 400 IU for body weight < 70 kg; 15 200 IU for body weight ≥ 70 kg). The first dose of LMWH was given at the emergency department under the supervision of a nurse. The patient or a family member was instructed how to administer LMWH at home. On the same day VKAs (phenprocoumon or acenocoumarol) were started, and titrated to an International Normalized Ratio (INR) between 2.0 and 3.0. The INR was monitored and VKA was titrated by the Dutch Thrombosis Services. LMWH was continued for at least 5 days, and was stopped by the Thrombosis Services if the INR was in the target range for two consecutive days. Patients with active malignancy could be treated with LMWH alone for a 6-month period, according to the guidelines [7]. This treatment decision was left to the treating physician.

Outcomes and follow-up

All patients were seen at the outpatient clinic at 1 week and 3 months after initial presentation. After 6 weeks of follow-up,
an additional telephone contact was planned. At each contact, the presence of clinical signs and symptoms suggestive of recurrent VTE or bleeding was assessed. Patients were instructed to contact their specialist for objective testing before the fixed appointments whenever clinical signs or symptoms suggestive of recurrent PE or DVT were present, or if a bleeding complication occurred.

The primary endpoint was objectively proven recurrent VTE during the 3 months of follow-up. Major bleeding and death within 3 months were defined as secondary endpoints.

Symptomatic recurrent VTE was the main efficacy parameter. Recurrent VTE was considered to be present if recurrent PE or DVT were documented objectively, or in the case of death for which PE could not be confidently ruled out as a contributory cause. The objective criterion for the diagnosis of recurrent PE was: a new intraluminal filling defect on spiral computed tomography (CT) or pulmonary angiography; cut-off of contrast material in a vessel > 2.5 mm in diameter on pulmonary angiography; a new perfusion defect involving at least 75% of a segment, with corresponding normal ventilation (i.e. a high-probability lung scan); a new non-diagnostic lung scan accompanied by documentation of DVT by ultrasonography or venography; or confirmation of a new PE at autopsy. The objective criterion for a new DVT was a new, non-compressible venous segment or a substantial increase (≥ 4 mm) in the diameter of the thrombus during full compression in a previously abnormal segment on ultrasonography; or a new intraluminal filling defect on contrast venography.

Major bleeding was the main safety outcome, and was defined as fatal bleeding, and/or symptomatic bleeding, in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of more than 2.0 g dL\(^{-1}\) (1.3 mmol L\(^{-1}\)), or leading to transfusion of more than two units of whole blood or red cells [23]. Clinically relevant bleeding episodes, not qualifying as major bleeding, were classified as clinically relevant non-major bleeding (e.g. epistaxis that required intervention, large hematoma visible on the skin, or spontaneous macroscopic hematuria).

Mortality was defined as death resulting from recurrent PE (fatal PE), fatal bleeding, cancer, or another established diagnosis. Information about the cause of death was obtained from autopsy reports or from a clinical report.

An independent adjudication committee consisting of two physicians not involved in the study evaluated all possible endpoints, i.e. recurrent VTE, major bleeding, or death. Any dispute was resolved by a third opinion. If no objective imaging of a suspected event was obtained, the event was evaluated on clinical grounds by the adjudication committee.

**Statistical analysis**

The primary endpoint was symptomatic recurrent VTE during 3 months of follow-up. We considered outpatient treatment to be effective if the upper limit of the 95% confidence interval (CI) of the incidence of recurrent VTE did not exceed a predefined margin. This predefined margin was based on incidences reported in the literature [6,24]. It was stated that VTE recurrence rates of patients treated at home should not be higher than rates found in patients treated in the hospital. Incidences of recurrent VTE up to 7% are reported in the literature [6,25]. We therefore defined outpatient treatment according to the predefined criteria as effective if the upper limit of the 95% CI did not exceed 7%.

A power calculation was performed on the assumption of an observed VTE recurrence in the study population of 3% [24]. To obtain an estimate of the incidence with a CI below 7%, a sample size of 257 patients was needed to achieve a power of 0.91 (one-sided binomial test). Allowing for a drop-out rate of 10%, a total of 280 patients with PE eligible for outpatient treatment had to be included. Exact 95% CIs were calculated around the observed incidences with Fisher's exact test. spss version 17.0 (SPSS, Chicago, IL, USA) was used for all analyses. The analyses were performed according to the intention-to-treat principle.

**Results**

**Study patients**

Between May 2008 and April 2010, a total of 581 consecutive patients with acute PE were screened with the exclusion criteria for outpatient treatment; 243 were not eligible for outpatient treatment according to the criteria described in Fig. 1.

A total of 338 patients were eligible for outpatient treatment; 41 patients were excluded for study reasons. This resulted in a total study population of 297 (51%) patients treated as outpatients (Fig. 1). Some of the patients (23%) were admitted to the hospital for < 24 h, mainly because CT scanning was not available at night. The mean duration of hospital admission in these patients was 19 h. The clinical baseline characteristics of these patients are shown in Table 2. The mean age was 55 years, and 26% of patients were older than 65 years; 58% of the patients were male, and 9% had an active malignancy.

**Treatment and follow-up**

All patients were treated with LMWH for at least 5 days, except for one patient, who received only 4 days of LMWH treatment, because of hemoptysis. In another patient, the LMWH treatment protocol was violated. This patient received the first dose of LWMH in the emergency department, but he did not continue the treatment at home. Although he finally received LMWH for at least 5 days, the LMWH treatment was interrupted for 48 h during the second and third day after the index event. In the majority of patients, initial LMWH therapy was followed by VKA treatment (Table 2). Of the patients, 6.1% were treated with long-term LMWH treatment alone, because of malignancies...
or known allergy to VKA. For three patients (1.0%), information on the type and duration of anticoagulant treatment was missing. The 3-month follow-up was completed for all patients.

Outcome events

Efficacy during the first week of treatment  One patient had recurrent PE during the first week (0.3%; 95% CI 0.008–1.9). In this patient, the LMWH treatment protocol had been violated (described above), because he did not use LMWH at home. He returned to the hospital at day 3 with increasing dyspnea; although no repeat CT scan was performed, this was adjudicated as an extension of the initial PE. He was admitted to the hospital for adequate anticoagulant therapy with therapeutic doses of LMWH and VKAs (Table 4). None of the patients receiving adequate anticoagulant treatment experienced a recurrent VTE event within 7 days of the initial event. No patient died of fatal PE during this period.

Efficacy during further follow-up  Between the second week and 3 months of follow-up, another five patients had recurrent VTE: recurrent PE in four patients, and DVT in one patient (Table 3). During the whole study period of 3 months of follow-up, six patients (2.0%; 95% CI 0.8–4.3) had a recurrent VTE, one of whom (0.3%; 95% CI 0.008–1.9) had an objectively proven recurrent DVT, and five of whom (1.7%; 95% CI 0.5–3.9) had recurrent PE, adjudicated on clinical grounds. In five of six patients adjudicated as having recurrent VTE, anticoagulant treatment was altered. The details are given in Table 4. None of the recurrent VTE events was fatal, and all patients recovered completely (Table 4).
Mortality

Three patients (1.0%; 95% CI 0.2–2.9) died during the study (Table 3). One patient died of fatal intracranial bleed at day 7. This intracranial bleed started while she was in the outpatient clinic for a predefined appointment; she died within 24 h. The second patient had a large abdominal muscle hematoma accompanied by a drop in hemoglobin level of 2.5 mmol L\(^{-1}\) at day 14, for which a short observation on the intensive care unit was needed; this patient recovered completely. Clinically relevant non-major bleeding occurred in 15 patients (5.1%; 95% CI 2.9–8.2). These non-major clinically relevant bleeds occurred between day 1 and day 66 (median, day 24) and consisted of five patients with large skin hematomas, six patients with macroscopic hematuria, three patients with hemoptysis, and one patient with an ovary bleed without significant drop in hemoglobin. In three patients with clinically relevant non-major bleeding, anticoagulant treatment was interrupted for 1 day: in one patient with hemoptysis, in one patient with a large skin hematoma, and in the patient with the ovary bleed.

Safety

Two patients (0.7%; 95% CI 0.08–2.4) had a major bleeding episode (Table 3). One patient had a fatal intracranial bleed at day 7. This intracranial bleed started while she was in the outpatient clinic for a predefined appointment; she died within 24 h. The second patient had a large abdominal muscle hematoma accompanied by a drop in hemoglobin level of 2.5 mmol L\(^{-1}\) at day 14, for which a short observation on the intensive care unit was needed; this patient recovered completely. Clinically relevant non-major bleeding occurred in 15 patients (5.1%; 95% CI 2.9–8.2). These non-major clinically relevant bleeds occurred between day 1 and day 66 (median, day 24) and consisted of five patients with large skin hematomas, six patients with macroscopic hematuria, three patients with hemoptysis, and one patient with an ovary bleed without significant drop in hemoglobin. In three patients with clinically relevant non-major bleeding, anticoagulant treatment was interrupted for 1 day: in one patient with hemoptysis, in one patient with a large skin hematoma, and in the patient with the ovary bleed.

Non-fatal major bleeding

One patient with a large skin hematoma, and in the patient with an ovary bleed

Major bleeding complications

Two patients (0.7%; 95% CI 0.08–2.4) had a major bleeding episode (Table 3). One patient died of fatal intracranial bleed at day 7. This intracranial bleed started while she was in the outpatient clinic for a predefined appointment; she died within 24 h. The second patient had a large abdominal muscle hematoma accompanied by a drop in hemoglobin level of 2.5 mmol L\(^{-1}\) at day 14, for which a short observation on the intensive care unit was needed; this patient recovered completely. Clinically relevant non-major bleeding occurred in 15 patients (5.1%; 95% CI 2.9–8.2). These non-major clinically relevant bleeds occurred between day 1 and day 66 (median, day 24) and consisted of five patients with large skin hematomas, six patients with macroscopic hematuria, three patients with hemoptysis, and one patient with an ovary bleed without significant drop in hemoglobin. In three patients with clinically relevant non-major bleeding, anticoagulant treatment was interrupted for 1 day: in one patient with hemoptysis, in one patient with a large skin hematoma, and in the patient with the ovary bleed.

Mortality

Three patients (1.0%; 95% CI 0.2–2.9) died during the study (Table 3). One patient died of fatal intracranial bleed at day 7, confirmed by autopsy. The cause of mortality in the two other patients was progressive metastatic pancreatic cancer (at days 29 and 59). The cause of death in the two patients with malignancy was clinically adjudicated by the treating physician. None of the patients died of fatal PE.

Discussion

This study evaluated the efficacy and safety of outpatient treatment of patients presenting with acute PE. Patients with acute PE were triaged in a standardized way, and eligible patients were treated as outpatients. The present study shows that outpatient anticoagulant treatment of patients selected with the exclusion criteria has a low risk for recurrent VTE: VTE recurred in 2% of patients, with the upper limit of the CI reaching 4.3%, which is lower than the predefined limit of 7%. None of the recurrences was fatal. None of the patients in the present study receiving adequate anticoagulant treatment experienced a recurrent VTE event within 7 days of the initial event, a period that equals the average duration of hospital admission for PE [26].

Comparison of the recurrence rate of 2.0% (95% CI 0.8–4.3) found in the present study with the VTE recurrence rate of 3.0% (95% CI 1.8–4.6) in a historical cohort of patients with PE treated in the hospital [24] shows almost identical rates, suggesting that the efficacy of LMWH treatment at home may be at least as good as the efficacy in the hospital. Moreover, our results are similar to outcomes in small prospective studies summarized in a systematic review [22], the results of a recently performed prospective cohort study [8], and the results of a large retrospective cohort [13] on outpatient treatment of PE. It is of note that our rate is considerably lower than the 6.2% found in the study of Kovacs et al. [12]. This discrepancy might be explained by the higher proportion of patients with malignancies (25% vs. 9%) in that study.

The rate of bleeding with the outpatient treatment was low in comparison with bleeding rates reported in the literature. In the present study, major bleeding occurred in 0.7%, and 5.1% of patients had non-major clinically relevant bleeding. In studies with comparable groups of patients, major bleeding rates in patients with PE treated at home varied between 0% and 2.8% [22]. Moreover, fatal bleeding occurred in only one patient (0.3%) in the present study. This compares well with the fatal bleeding rates of 0.3–0.6% in unselected patients with PE treated in the hospital [24,27].

In this study, a simple set of exclusion criteria was used to select patients for outpatient treatment. The choice of these criteria was reinforced by former research [12]. The criteria are pragmatic, easy to use at the bedside, quick to perform, and cheap. In this study, where predefined exclusion criteria were used, 51% of patients with PE could be treated out of the hospital, which is comparable to the 51–55% found in two large retrospective studies using comparable criteria [11,12]. In the literature, the use of ‘subjective items’ has been criticized [28]. However, this study shows that physicians guided by the simple bedside criteria are well able to distinguish low-risk patients who are eligible for outpatient treatment. In addition, comparable sets of criteria have been used safely in different cohorts from different countries [9,10,12,19–21].

Two other approaches have recently been suggested for selecting patients for outpatient treatment: the Pulmonary Embolism Severity Index (PESI) (NTCO0425542) [29] and NT-proBNP [8]. The predictive values of the PESI and NT-proBNP have been derived from unselected cohorts of patients with PE treated in the hospital [30,31]. A large cohort study with unselected patients treated for PE in the hospital demonstrated that patients with PE and low PESI scores (classes I and II) have a risk of 90-day mortality of 1.2% [29]. A recent meta-analysis showed that unselected patients with low NT-proBNP levels have a 30-day mortality of 1.3% [32]. The predictive value of the PESI and NT-proBNP in patients preselected with pragmatic exclusion criteria is currently unknown. In addition, these two selection methods are validated on short-term mortality, but our data showed that...
short-term mortality in preselected groups who are potentially eligible for outpatient treatment is very low (1.0%).

This study had strengths and limitations that should be addressed. To our knowledge, this is the largest trial in patients with acute PE who were treated as outpatients within 24 h after the diagnosis of PE. The inclusion of consecutive patients and the absence of loss to follow-up mean that selection bias is not an issue in the present study [33].

One limitation of the study is that the endpoint ascertainment could not be blinded, owing to the single-arm design. However, ascertainment of both the exposure (PE) and the outcome (recurrent VTE) was performed according to predefined criteria, which minimizes the risk of information bias.

The reported recurrence rate of 2% could be an overestimation, because in the five patients who were centrally judged as having recurrent PE, no objective imaging was performed. These five patients were centrally adjudicated as having recurrent PE because of the clinical signs suggestive of recurrent PE and/or the local decision to change anticoagulant therapy. The central adjudication committee was conservative on this, to avoid an underestimation of the recurrence rate. Another
limitation is that 23% of patients had to stay in the hospital for up to 24 h for logistic reasons.

Finally, we initially considered a randomized study design with random allocation to inpatient or outpatient treatment, but concluded that this was not feasible, owing to the very large sample size that would have been needed. Instead, a single-arm clinical trial was performed with predefined triaging of patients and careful standardized follow-up in all patients according to predefined criteria for assessing and adjudicating recurrent events and bleeding. Such a single-arm trial is a valid instrument with which to evaluate treatment in a population, provided that consecutive patients are included and all patients receive standardized triaging, to avoid investigator bias.

In conclusion, outpatient treatment of acute PE may be effective and safe in patients selected with the predefined and easy-to-use criteria, on the basis of the observed low recurrence, mortality and bleeding rates. In view of the single-arm trial design, these results have to be confirmed in a randomized controlled trial.

Addendum


Disclosure of Conflict of Interests

This study was partially supported by an unrestricted research grant from G.S.K., the Netherlands BV. G.S.K. had no influence on the design and writing of the protocol, collection of data, performance of the analysis of the study results, or writing of the manuscript. M.V. Huisman reports receiving research grants from G.S.K. and Actelion, and speaking or consulting for Bayer, Boehringer Ingelheim, and Pfizer. The other authors state that they have no conflict of interest.

Appendix

Hestia Study Group

In addition to the authors, the following hospitals and investigators participated in this study:


Independent Adjudication Committee

H. ten Cate, Maastricht University Medical Center, Maastricht. K. Hamulya: Maastricht University Medical Center, Maastricht. V. Gerdes: Slotervaart Hospital, Amsterdam.

References

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