Treatment of acute pulmonary embolism as outpatients or following early discharge
A systematic review

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Summary
The purpose of this systematic review is to test the hypothesis that carefully selected low-risk patients with acute pulmonary embolism (PE) can safely be treated entirely as outpatients or after early hospital discharge. Included articles were required to describe inclusion or exclusion criteria and outcome of patients treated for PE. Early hospital discharge was defined as an average hospital stay ≤ 3 days. Six investigations included patients with PE who were treated entirely as outpatients; two investigations included patients with PE who were treated after early discharge. All investigations included only low-risk patients or patients with small or medium sized PE. Outcome after 3-46 months in patients treated entirely as outpatients showed recurrent PE in 0% to 6.2% of patients, major bleeding in 0% to 2.8% with one death from an intracerebral bleed. Definite death from PE did not occur; but there was one possible death from PE. Outcome in three months in patients treated after early discharge showed no instances of recurrent PE. Major bleeding occurred in 0% to 3.7% of patients. There were no deaths from PE, but there was one death from bleeding. In conclusion, outpatient therapy of acute PE is probably safe in low-risk, carefully selected compliant patients who have access to outpatient care if necessary. Such outpatient treatment would be cost-effective.

Keywords
Pulmonary embolism, deep venous thrombosis, outpatient treatment

Introduction
Outpatient treatment of deep venous thrombosis (DVT) with low-molecular-weight heparin (LMWH) followed by vitamin K antagonists was shown in 1996 to be safe and effective in carefully chosen patients (1, 2). Subsequent investigations supported the outpatient approach to the treatment of DVT (3–9). Patients with pulmonary embolism (PE) were excluded from most investigations of outpatient treatment of DVT or treatment after early discharge (1–3, 7–9). PE is a more ominous and potentially fatal form of venous thromboembolism (VTE) than DVT (10). The risk of fatal recurrent PE in patients treated for PE is greater than the risk of fatal PE in patients treated for DTV (1.5% vs. 0.4%) (11). By 2002, patients with DVT who also had PE were sometimes included (12). Several investigations of the outpatient treatment or early discharge treatment of acute PE have now been reported. The British Thoracic Society in 2003 made a grade C recommendation that the current organization for outpatient management of DVT should be extended to include stable patients with PE (13). However, questions remain of whether outpatient treatment is appropriate for PE, and if so, which patients are suitable candidates (10). The American College of Chest Physicians (ACCP) Clinical Practice Guidelines (8th Edition) indicated that the feasibility of treating a substantial proportion of patients with symptomatic PE with LMWH at home is supported by data in patients with PE included in randomized trials and data in observational studies, but no recommendation was made (14). The purpose of this systematic review is to test the hypothesis that carefully selected low-risk patients with acute PE can safely be treated in this manner.

Methods
We used established methods for systematic review (15–17). A broad search of the literature in all languages was performed incorporating both electronic and manual components. The elec-
Electronic search was performed using PubMed, which includes MEDLINE, OLDMEDLINE, OVID and we also searched Embase. The dates of the searches were from 1964 through March 2008 with MEDLINE and 1991 through June 2008 with Embase. We used combined medical subject headings (MeSH). Combined search terms were: Pulmonary embolism matched with outpatient treatment, ambulatory management, ambulatory, ambulatory treatment, outpatient, home treatment, early discharge, office treatment, community based treatment, treatment in the community setting, home management home care. Manual reference checks of recent reviews and all original investigations were performed to supplement the electronic searches.

**Study selection for data extraction**

Two reviewers independently screened the abstracts and titles of the search results and eliminated articles only if they clearly did not relate to outpatient treatment of PE. Inclusion required that PE and recurrent PE or DVT on follow-up were objectively confirmed. Inclusion also required that patients with PE were treated entirely as outpatients or discharged from hospital after an average of ≤3 days. Articles that described results of patients discharged early were required to describe the length of hospital stay. Articles were required to describe inclusion or exclusion criteria, and outcome of patients treated for PE. Studies may have been prospective or retrospective. In order to obtain a broad impression of results of outpatient treatment of PE, we included investigations of selected populations (cancer patients) as well as unselected populations. We included studies with various exclusion criteria and studies that used various anticoagulant regimens.

Articles were excluded if patients with PE were included among those with DVT without giving specific results of those with PE. One study was excluded because patients were treated in a “hospital in the home”, that had several aspects of hospital care (18). We also excluded abstracts, case reports, comments, reviews, and case-series with ≤10 patients. Full articles were obtained if a determination of exclusion criteria could not be made from the title or the abstract.

Information collected in each article included number of patients, study characteristics, inclusion criteria, exclusion criteria, treatment, length of follow-up, methods of diagnosis of PE, methods of diagnosis of PE or DVT on follow-up, definitions of major bleeding, incidence of recurrent PE, major bleeds, death from PE, and death from bleeding.

**Data retrieval**

A flow diagram outlining the systematic review process is provided (Fig. 1). The literature search identified 935 citations for screening. Of these, 928 were rejected for the reasons shown in Figure 1 after reviewing the titles, abstracts, or the entire article. Seven investigations met the inclusion criteria.

**Statistical analysis**

95% confidence intervals (CI) were calculated using calculator for confidence intervals of relative risk (www.sign.ac.uk/methodology/risk.xls).

## Results

Six investigations were prospective (19–24) and one was retrospective (25) (Table 1). Six investigations included patients with PE who were treated entirely as outpatients (19, 21–25). In one of these, patients were maintained an average of five days in a “patient hotel close to the hospital” (21). Two investigations included patients with PE who were treated after hospitalization ≤3 days (20, 22).

Inclusion and exclusion criteria are shown in Table 1. Methods of diagnosis and definitions of major bleeding are shown in Table 2. All investigations included only low-risk patients which was specifically stated (19, 20) or described as small or medium-sized (21) or submassive PE (25), or with exclusions indicative of high risk such as hemodynamic instability (22, 25), high risk of bleeding or active bleeding (19–25), poor oxygenation (20, 22, 24, 25), renal insufficiency (19, 23, 24) or low platelets (19, 24). Additional frequent exclusions were for concomitant illness requiring hospitalization (20, 22–24), intense pain (21–25), requirement for parenteral drugs (20, 22-25), and likelihood of poor compliance (20, 22, 23, 25).

Treatment was usually with LMWH followed by oral anticoagulants, although some received intravenous unfractionated heparin (UFH) during a short admission (22).

Outcome within one week after outpatient treatment was described in one investigation (21). A new perfusion defect was described in nine of 100 patients (9%) (21). Hospitalization was required in five patients (21).
<table>
<thead>
<tr>
<th>First author, year (Reference)</th>
<th>No. of patients</th>
<th>Study characteristics</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer 2003 (19)</td>
<td>43</td>
<td>Outpatients</td>
<td>Low risk (Geneva criteria*)</td>
<td>Contraindication to anticoagulation</td>
<td>Nadroparin 171 U/kg 5–10 days Oral anticoagulation 6–12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Contraindication to LMWH or UFH History of drug addiction, Non-compliant Body weight &gt;110 kg Psychiatric conditions Creatinine clearance &lt; 30 ml/min Platelets &lt;120 x10^3/µl Fibrinolytic therapy Treatment with oral anticoagulants &lt; 24 hours prior to study.</td>
<td></td>
</tr>
<tr>
<td>Davies 2007 (20)</td>
<td>156</td>
<td>Early discharge (Median hospital stay 1 day (0–3 days)</td>
<td>Low risk Diagnosis ≤72 hours Age &gt;18 years</td>
<td>Hospitalized for concomitant illness Monitoring required O2 therapy Intravenous drugs Previous or recurrent PE on anticoagulants Co-existing major DVT Bleeding disorder or active bleeding, Pregnancy Poor compliance (i.e elderly, infirm, immobile)</td>
<td></td>
</tr>
<tr>
<td>Olsson 2006 (21)</td>
<td>100</td>
<td>Outpatients (hotel) median stay 5 days.</td>
<td>Small or medium sized PE on VQ scan</td>
<td>Extensive PE (&gt; 40% lung perfusion), Ancillary lung disease (&gt; 20% of lung parenchyma), Intense pain Post surgery Active bleeding Logistic and technical reasons</td>
<td></td>
</tr>
<tr>
<td>Kovacs 2000 (22)</td>
<td>108</td>
<td>Outpatients (hotel) median stay 5 days.</td>
<td>All except those with exclusion criteria</td>
<td>Hospitalized for other medical condition Active or high-risk bleeding Haemodynamic instability Pain requiring parenteral narcotics Required O2 Age &lt;18 years Poor compliance</td>
<td></td>
</tr>
<tr>
<td>Siragusa 2005 (23)</td>
<td>36</td>
<td>All cancer patients Outpatient</td>
<td>All except those with exclusion criteria</td>
<td>Concomitant illness that required hospitalization Poor compliance, High risk of bleeding or active bleeding Renal insufficiency Acute anemia Pain requiring parenteral narcotics</td>
<td></td>
</tr>
<tr>
<td>Wells 2005 (24)</td>
<td>90</td>
<td>Outpatient</td>
<td>All except those with exclusion criteria</td>
<td>Active bleeding or high risk of bleeding Stroke ≤10 days Gastrointestinal bleeding ≤14 days Platelets &lt;75 x10^3/µl Asymptomatic DVT Age&lt;18 years No fixed address Previous heparin induced thrombocytopenia Renal failure (creatinine &gt;2.3 mg/dl) Treatment with UH or LMWH &gt;36 hours Hypotension Required O2 Pain requiring intravenous narcotics</td>
<td></td>
</tr>
<tr>
<td>Ong ** 2005 (25)</td>
<td>60</td>
<td>Outpatient</td>
<td>Submassive PE</td>
<td>LMWH tinzaparin (175 U/kg daily) or dalteparin (200 U/kg daily) &gt;5 days warfarin</td>
<td></td>
</tr>
</tbody>
</table>

*Wicki Geneva criteria = Wicki et al. (31). **Retrospective. All others were prospective. VQ = ventilation perfusion lung scan; LMWH = low-molecular-weight heparin; UH = unfractionated heparin; PE = pulmonary embolism; DVT = deep venous thrombosis; O2 = oxygen.
Outcome after 3–46 months in patients treated entirely as outpatients showed recurrent PE in 0% to 6.2% of patients (19, 21–24) (Table 3). Major bleeding, in five investigations that reported bleeding, occurred in 0–2.8% of patients (19, 21–24). Definite death from PE did not occur (19, 21, 22, 24, 25). One patient died from an intracerebral bleed (21).

Outcome in three months in patients treated after discharge ≤3 days showed no instances of recurrent PE (20, 22) (Table 4). Major bleeding occurred in 0.6–3.7% of patients (20, 22). There were no deaths from PE (20, 22). One death from bleeding occurred in a patient who also had septicemia and neutropenia (20).

Discussion

All investigations included only patients in whom the risks of death from PE were low and the risks of bleeding from treatment were also low based on various methods of assessment and exclusion criteria as listed in Table 1. Some patients were treated entirely as outpatients and some were treated in-hospital for ≤3 days. Treatment regimens also varied. In this sense, there was large heterogeneity in the investigations. All of the data are from observational studies. Most were prospective (19–24), but one retrospective investigation was included (25). None of the investigations randomized patients for outpatient versus inpatient treatment. Within this context, outpatient treatment of acute PE was reported in 410 patients (19, 21–25).
and home treatment after ≤3 days hospitalization was reported in 183 patients (20, 22). Death from PE did not occur among 557 patients in whom the cause of death was reported (19–22, 24, 25). There were two deaths from bleeding among these 557 patients (19–22, 24, 25). Recurrent PE was observed only among those treated as outpatients (0–6.2%) (19, 21–24). Recurrent PE was not observed among those treated after early discharge (20, 22). Major bleeding occurred in 0–3.7% (19–24). There is a clear need for a randomized clinical trial comparing results of in-patient with outpatient management of low-risk patients with acute PE.

The average length of hospital stay for patients with acute PE throughout the United States decreased from 14 days in 1979 to 8.5 days in 1999 (26). The median length of hospital stay for PE in 2002 in Pennsylvania was six days (27). We excluded investigations in which the average length of stay was four days (range 0–17 days) (28) and we excluded the early discharge arm of the investigation by Ong et al. (25) in which the average length of stay was 5.7 days (range 2–19 days).

The proportion of hospitalized patients with acute PE who were assessed as low risk has been reported as 34% (29), 47% (30) and 67% (31). Assuming a cost difference of $4,500 between inpatient and outpatient treatment, and an annual PE incidence of 126,000 cases, up to $284 million per year could be saved in the United States if half of the patients were treated as outpatients (30).

Based on the available data, it appears that outpatient treatment of acute PE is safe providing the patient is at low risk of an adverse outcome including death, a recurrent thromboembolic event, or major bleeding. Risk stratification facilitates identification of high-risk patients who should not be treated as outpatients and may be helpful in guiding initial and long-term management (32). Wicki et al. identified six independent predictors of death, recurrent thromboembolic events, or major bleeding in three months (31) (Table 5). Aujesky et al. developed a prediction rule to identify low risk patients with PE based on 10 factors (29) (Table 5). Aujesky et al. also developed a Pulmonary Embolism Severity Index (PESI) for low risk of death at three months that included 11 factors (30) (Table 5). Additional tools for risk stratification include electrocardiography, echocardiography, cardiac biomarkers, and chest computed tomography (32). Reasons for requiring inpatient treatment, not included in the prognostic models but used by some, were large PE based on the size of the perfusion scan defect, high risk of bleeding or active bleeding, low platelet count, concomitant illness, intense pain, requirement for parenteral drugs, and likelihood of poor compliance.

In conclusion, outpatient therapy of acute PE is probably safe in low-risk, carefully selected compliant patients who have access to outpatient care if necessary. Appropriate selection of patients for outpatient treatment would be cost effective.

<table>
<thead>
<tr>
<th>First author, year (Ref.)</th>
<th>Follow-up (months)</th>
<th>Recurrent PE (%)</th>
<th>95% CI</th>
<th>Major bleed (%)</th>
<th>95% CI</th>
<th>Death from PE (%)</th>
<th>95% CI</th>
<th>Death from bleeding (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davies 2007 (20)</td>
<td>3</td>
<td>0/156 (0)</td>
<td>0–2.3</td>
<td>1/156 (0.6)</td>
<td>0.2–3.5</td>
<td>0/156 (0)</td>
<td>0–2.3</td>
<td>1/156 (0.6)</td>
<td>0.2–3.5</td>
</tr>
<tr>
<td>Kovacs 2000 (22)</td>
<td>3</td>
<td>0/27 (0)</td>
<td>0–12.3</td>
<td>1/27 (3.7)</td>
<td>0–9–18.3</td>
<td>0/27 (0)</td>
<td>0–12.3</td>
<td>0/27 (0)</td>
<td>0–12.3</td>
</tr>
</tbody>
</table>

CI = confidence interval.

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### Table 5: Predictors of low risk according to pulmonary embolism prognostic models.

<table>
<thead>
<tr>
<th>Predictor (31)</th>
<th>Point Score*</th>
<th>Clinical Prediction Rule (29) Predictor**</th>
<th>Pulmonary Embolism Severity Index (30)</th>
<th>Point Score***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>2</td>
<td>Age ≥70 years</td>
<td>Age (years)</td>
<td>1 / year</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
<td>History of cancer</td>
<td>Male</td>
<td>10</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>1</td>
<td>Heart failure</td>
<td>Cancer (History or active)</td>
<td>30</td>
</tr>
<tr>
<td>Syst BP &lt;100mmHg</td>
<td>2</td>
<td>Chronic lung disease</td>
<td>Heart failure</td>
<td>10</td>
</tr>
<tr>
<td>P_aO_2&lt;8 kPa</td>
<td>1</td>
<td>Chronic renal disease</td>
<td>Chronic lung disease</td>
<td>10</td>
</tr>
<tr>
<td>DVT Ultrasound</td>
<td>1</td>
<td>Cerebral vascular disease</td>
<td>Pulse ≥110/min</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Syst BP &lt;100 mmHg</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resp rate ≥30/min (with or without O_2)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arterial O_2 sat &lt;90%</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Altered mental status (disorientation, stupor, lethargy, coma)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Arterial O_2 sat &lt;90%</td>
<td>20</td>
</tr>
</tbody>
</table>

* Low risk = score ≤2 (31). **Low risk = none of these factors (29). ***Low risk = score ≤85 (30). Syst = systolic, sat = saturation, PE = pulmonary embolism, DVT = deep venous thrombosis, resp = respiratory, O_2 = oxygen, yr = year.
References