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PIRAN, Siavash, *et al.*

### Abstract

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### Reference

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## Regular Article

# Outpatient treatment of symptomatic pulmonary embolism: A systematic review and meta-analysis<sup>☆</sup>

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## ABSTRACT

**Background:** Patients with acute deep vein thrombus (DVT) can safely be treated as outpatients. However the role of outpatient treatment in patients diagnosed with a pulmonary embolism (PE) is controversial. We sought to determine the safety of outpatient management of patients with acute symptomatic PE.

**Materials and Methods:** A systematic literature search strategy was conducted using MEDLINE, EMBASE, the Cochrane Register of Controlled Trials and all EBM Reviews. Pooled proportions for the different outcomes were calculated.

**Results:** A total of 1258 patients were included in the systematic review. The rate of recurrent venous thromboembolism (VTE) in patients with PE managed as outpatients was 1.47% (95% CI: 0.47 to 3.0%; I<sup>2</sup>: 65.4%) during the 3 month follow-up period. The rate of fatal PE was 0.47% (95% CI: 0.16 to 1.0%; I<sup>2</sup>: 0%). The rates of major bleeding and fatal intracranial hemorrhage were 0.81% (95% CI: 0.37 to 1.42%; I<sup>2</sup>: 0%) and 0.29% (95% CI: 0.06 to 0.68%; I<sup>2</sup>: 0%), respectively. The overall 3 month mortality rate was 1.58% (95% CI: 0.71 to 2.80%; I<sup>2</sup>: 45%). The event rates were similar if employing risk stratification models versus using clinical gestalt to select appropriate patients for outpatient management.

**Conclusions:** Independent of the risk stratification methods used, the rate of adverse events associated with outpatient PE treatment seems low. Based on our systematic review and pooled meta-analysis, low-risk patients with acute PE can safely be treated as outpatients if home circumstances are adequate.

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## Introduction

Patients with acute deep vein thrombus (DVT) can safely be treated as outpatients [1–4]. Outpatient treatment of DVT is recommended with grade 1B evidence in the most recent American College of Chest Physicians (ACCP) guidelines [5]. However the ACCP guidelines and other scientific societies have not firmly recommended outpatient therapy for patients with low-risk acute pulmonary embolism (PE) [5,6]. Clinicians appear reluctant to discharge PE patients due to a

perceived lack of high quality data regarding both appropriate patient selection and outcomes with home treatment [7].

Several studies have reported that outpatient management or early discharge of patients with acute PE is safe and effective [8–13]. Two systematic reviews suggested that patients with acute PE treated as outpatients had low incidences of major bleeding, recurrent venous thromboembolism (VTE), and mortality [14,15]. However the quality of the included studies was low and subsequent and recent larger observational studies and randomized control trials were not included [8,11,16,17]. More recently, two additional systematic reviews of the outpatient management of acute symptomatic PE were published [18,19]. However the first review did not include studies of patients with acute PE managed with early discharge and did not perform a meta-analysis [18]. The last review included both retrospective and prospective studies which lower the overall quality of evidence from which the event rates are derived [7,19].

In this systematic review and meta-analysis we sought to determine the feasibility and safety of outpatient treatment (including early discharge). Furthermore, we attempted to compare the outcome event rates when risk stratification models are applied versus using clinical gestalt to select appropriate patients for outpatient

**Abbreviations:** ACCP, American College of Chest Physicians; CI, Confidence Interval; CTPA, CT Pulmonary Angiogram; DVT, Deep vein thrombus; EBM, Evidence Based Medicine; ICH, Intracranial Hemorrhage; LMWH, Low Molecular Weight Heparin; NT-proBNP, N-terminal Pro-hormone of Brain Natriuretic Peptide; PE, Pulmonary Embolism; PESI, Pulmonary Embolism Severity Index; RCTs, Randomized Controlled Trials; UFH, Unfractionated Heparin; VTE, Venous Thromboembolism; V/Q, Ventilation-perfusion.

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management. Finally, short-term (<14 days) outcome event rates were evaluated.

## Materials and Methods

### Search Strategy

We conducted a systematic literature search to identify potential studies on MEDLINE (1950 to week 4 of June 2012), EMBASE (1980 to end of June 2012), the Cochrane Central Register of Controlled Trials, and all evidence-based medicine reviews (e-Table 1 – online). We also sought publications through a hand-search of potentially relevant journals and International Society of Thrombosis and Haemostasis conference proceedings (2003–2011). We also reviewed the references of included studies and previous systematic reviews for additional potential studies. There were no restrictions on language or publication year.

### Study Selection

Two investigators (S.P. and M.C.) independently screened the titles and abstracts of articles to find potentially relevant articles. Two investigators (S.P. and M.C.) then reviewed potentially relevant articles in full length to ensure that they satisfied these criteria: 1) Prospective enrollment of patients with objectively confirmed symptomatic PE. Pulmonary embolism was diagnosed with a high-probability ventilation-perfusion (V/Q) lung scan or a segmental or larger pulmonary artery filling defect on either computed tomography (CTPA) or pulmonary angiography; 2) patients received treatment for a minimum of 3 months with anticoagulation therapy (vitamin K antagonist, weight-based or adjusted-dose unfractionated heparin, weight-based or fixed dose low molecular weight heparin (LMWH)); 3) all outcomes categories were reported including VTE recurrence, major bleeding, fatal PE, fatal intracranial hemorrhage (ICH). We included randomized controlled trials and prospective cohort studies. We excluded review articles, case reports, letter to editor, editorials, retrospective, and unrelated studies. The clinical course of patients with suspected pulmonary embolism. Moreover, we did not include studies if outcome data was not separately reported (or was unavailable) for patients with PE. Appendix Fig. 1 (online) details the Study Selection Flow chart.

### Outcome Measures

Recurrent VTE (recurrent PE and DVT) was defined as a new segmental mismatch on V/Q scan, a new intra-luminal filling defect on CTPA or pulmonary angiography, or a new non-compressible segment on deep leg vein. The rate of recurrent VTE used to determine the safety of outpatient treatment of acute PE was  $\leq 3\%$  during a 3-month follow-up period [20,21]. Major bleeding was defined as bleeding that required transfusion of 2 or more units of packed red blood cells or caused a fall in hemoglobin of 20 g/L or more, involved a critical site (e.g. intracranial), or was fatal [22] or as defined by the investigators of the individual studies.

### Quality Assessment

We assessed the methodological quality of the included studies using the Risk of Bias Assessment Tool from the Cochrane Handbook for randomized trials [23] and the Newcastle-Ottawa Quality Assessment scale for observational studies [24].

### Data Synthesis and Statistical Analysis

Ninety-five percent confidence intervals (95% CI) were calculated for each rate using the averaged, inverse variance-weighted estimates from each study. We calculated the pooled proportions, via random effects model, for the different outcomes at 3-months of follow-up

(Stats Direct software, version 2.7.9). Pooled proportion meta-analysis was also performed for short-term outcomes for up to 14 days of follow-up. Sensitivity analyses (RCTs vs. cohort studies; outpatients vs. early discharge) were conducted to explore heterogeneity. The  $I^2$  statistic was used to estimate total variation among the pooled proportions. An  $I^2$  value <25% was considered low level of heterogeneity; 25–50% was moderate, and >50% was considered high level [25].

## Results

We identified 1564 citations in our literature search and 16 articles were found to be potentially eligible (Appendix Fig. 1 – online). Five of these articles were then excluded. Three articles because the outcome measures were not reported specifically for patients with acute PE [26–28] and two because patients had not been managed as outpatients [29,30]. The remaining 11 studies were included in our systematic review. Eight were prospective cohort studies [8,11–13,31–34] and 3 were randomized controlled trials (RCTs) [16,17,35]. Furthermore, 2 studies did not report outcomes at 3 months and could not be used in our pooled meta-analysis [12,13].

Table 1 shows the baseline characteristics of the included studies. A total of 1258 patients were included in the systematic review. Eight of the studies exclusively included patients that were treated entirely as outpatients. Two studies included patients that were discharged early [16,32] and 1 study reported early discharge and outpatient groups separately [34]. Early discharge was generally defined as inpatient stay of 1–3 days [16,32]. Most studies treated patients with intravenous unfractionated heparin or subcutaneous LMWH in combination with a vitamin K antagonist.

Outcome events in the individual studies and the pooled event rates during the 3 months of follow-up are reported in Tables 1 and 2, respectively. The rate of recurrent VTE in patients with PE managed as outpatients was 1.47% (95% CI: 0.47 to 3.0%;  $I^2$ : 65.4%) during the 3 months follow-up period. The pooled rate of fatal PE was 0.47% (95% CI: 0.16 to 1.0%;  $I^2$ : 0%). The rates of major bleeding and fatal ICH were 0.81% (95% CI: 0.37 to 1.42%;  $I^2$ : 0%) and 0.29% (95% CI: 0.06% to 0.68%;  $I^2$ : 0%), respectively. The overall mortality rate was 1.58% (95% CI: 0.71 to 2.80%;  $I^2$ : 45%). Sensitivity analyses assessing event rates according to study design (cohort vs. RCT) or type of management (outpatients vs. early discharge) did not significantly alter heterogeneity of pooled estimates (data not shown).

Five of the 11 studies used risk stratification models to select patients for outpatient treatment and the remainder used clinical gestalt (i.e. general impression that PE patient can be treated with outpatient therapy). The studies that used clinical gestalt utilized specific exclusion criteria to select low-risk patients for outpatient management. (e-Table 2– online). The pooled rates of VTE recurrence for the clinical gestalt subgroup versus the risk stratification subgroup were 1.88% (95% CI: 0.11% to 5.73%;  $I^2$ : 74.4%) and 1.4% (95% CI: 0.4% to 2.9%;  $I^2$ : 45%), respectively. Similarly, the pooled rate of major bleeding for patients stratified using clinical gestalt was 0.62% (95% CI: 0.059% to 1.79%;  $I^2$ : 14.7%) compared to 0.94% (95% CI: 0.4% to 1.8%;  $I^2$ : 25%) for patients identified using a risk stratification model.

Short term outcomes were reported in 5 studies for follow up period of <14 days (Table 3). A total of 552 patients were included in these subgroup analyses. Pooled event rates for <14 days of follow-up are reported in Table 4. The pooled rate of VTE recurrence was 0.28% (95% CI: 0.013% to 0.89%;  $I^2$ : 0%) during the short-term follow-up period. The short term pooled risk of major bleeding was 0.46% (95% CI: 0.022% to 1.46%;  $I^2$ : 30%). The pooled overall mortality rate was 0.41% (95% CI: 0.006% to 1.46%;  $I^2$ : 44%).

The quality of the included studies is depicted in e-Tables 3 and 4 (on-line only). Two out of the 3 RCTs reported adequate sequence generation and allocation concealment (e-Table 3) [23]. Patients and physicians were blinded in one study [35]. All 3 trials addressed incomplete outcome data and were free of selective outcome reporting. All

**Table 1**

Baseline Characteristics and Three Month Outcomes of the Studies Included in the Systematic Review.

Study	Design	N	Malignancy (%)	Risk Stratification	Management	Mortality (%)	Fatal PE (%)	Fatal ICH (%)	VTE Recurrence (%)	Major Bleeding (%)
Agterof, 2010	Cohort	152	20 (13.2)	Low NT-proBNP (<500 pg/mL)	Outpatient	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Aujesky, 2011	RCT	171	1 (1)	PESI (Class I or II)	Outpatient	1 (0.6)	0 (0)	0 (0)	1 (0.6)	3 (1.8)
Beer, 2003	Cohort	43	NA	Geneva Score (Score ≤2)	Outpatient	0 (0)	0 (0)	0 (0)	1 (2.3)	0 (0)
Davies, 2007	Cohort	157	NA	Clinical gestalt	Early discharge	3 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)
Kovacs, 2000	Cohort	108	24 (22.2)	Clinical gestalt	Outpatient and early discharge	4 (3.7)	0 (0)	0 (0)	6 (5.6)	2 (1.9)
Olsson, 2006	Cohort	102	NA	Clinical gestalt	Outpatient	NA	NA	NA	NA	NA
Otero, 2010	RCT	72	6 (4.5)	Uresandi score >2	Early discharge	3 (4.2)	1 (1.4)	0 (0)	2 (2.8)	1 (1.4)
Rodríguez-Cerrillo, 2009	Cohort	30	4 (13.3)	Clinical gestalt	Outpatient	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Siragusa, 2005	Cohort	36	36 (100)	Clinical gestalt	Outpatient	NA	NA	NA	NA	NA
Wells, 2005	RCT	90	NA	Clinical gestalt	Outpatient	3 (3.3)	0 (0)	0 (0)	2 (2.2)	0 (0)
Zondag, 2011	Cohort	297	28 (9.4)	Hestia criteria	Outpatient	3 (1)	0 (0)	1 (0.33)	6 (2)	2 (0.67)

NA = Not Available, PE = Pulmonary Embolism, PESI = Pulmonary Embolism Severity Index, RCT = Randomized Controlled Trial, VTE = Venous Thromboembolism.

prospective cohort studies were adequately representative and had adequate follow-up duration (e-Table 4). One study did not address the number of patients lost to follow up and did not have criteria for defining the outcomes [31]. Moreover, another study only defined major bleeding [33].

## Discussion

The results of our systematic review suggest that the short term and long-term (up to 3 months) rates of adverse outcomes are low and patients with low-risk acute symptomatic PE can safely be treated at home. Furthermore, both clinical gestalt and risk stratification models appear to be able to effectively and safely identify low risk patients with acute PE that can be managed as outpatients.

The risk of recurrent VTE, major bleeding episodes and overall mortality after 3 months of follow-up were low in our study with point estimates of 1.47% (95% CI: 0.47 to 3.0%), 0.81% (95% CI: 0.37 to 1.42%) and 1.58% (95% CI: 0.71 to 2.80%) respectively. Ideally, these rates should be compared to low-risk patients that were hospitalized for the initial management of their acute PE. Unfortunately, only two RCTs compared these risks in patients with acute PE managed as in or out-patients [16,17]. Both RCTs used a risk stratification model (PESI and Uresandi) to identify low risk patients. One of the RCTs used several other clinical criteria in addition to the PESI to identify low-risk patients for outpatient management [17] (e-Table 2). Of note, the PESI was derived to predict 30-day all cause mortality but does not include PE-related mortality or VTE recurrence [7]. Nonetheless, the event rates reported in our study are similar to those reported in the RCTs, pooled rates of recurrent VTE, major bleeding and overall mortality in low-risk hospitalized patients with acute PE within the two RCTs (n = 228) were 1.26 (95% CI: 0.22 to 7.2%), 0.73 (95% CI: 0.071 to 3.86) and 3.67 (95% CI: 0.021 to 15.15). Furthermore, the risk of VTE

reported in our study is lower than the previously reported pooled rate of recurrent VTE in a meta-analysis of RCTs on anticoagulant therapy for VTE combining patients managed as in- and out-patients (3.6% (95% CI: 2.3% to 5.0%)) [36]. Similarly, the risk of fatal PE in our study is 0.47 (95% CI: 0.16 to 1.0%) which is also lower than the fatal PE rates reported (1.3% (95% CI: 0.9% to 1.7%)) in the systematic review combining all VTE patients. This suggests that a subgroup of patients with low-risk acute PE identified using either clinical gestalt or risk stratification could be effectively and safely managed completely as outpatients.

Low-risk patients could represent up to 50% of patients diagnosed with acute PE [9,17,37]. This is particularly important given that new oral direct anticoagulants are now approved for the treatment of PE in several jurisdictions which further simplify and enable the outpatient management of PE. Moreover, the implementation of outpatient management strategies may reduce the length of hospital stay, which would be cost-effective [7]. Hospitalization represents more than 50% of the costs associated with a new diagnosis of acute PE in the US [38]. A study examined the outcomes and resource utilization for PE, from a nationwide USA inpatient sample, and reported that between 1998 and 2005 the length of hospital stay decreased from 9.4 days to 8.6 days though the total hospital charges increased from \$25,293 to \$43,740 [39]. In another systematic review, patients with common medical conditions reported increased satisfaction with admission avoidance via hospital at home [40]. However, home circumstances need to be adequate [5]. Patients who prefer the security of the hospital to the convenience and comfort of home are likely to choose hospitalization over home treatment [5]. Finally, the practice of outpatient management may also help prevent the occurrence of potential adverse drug reactions associated with hospital admissions thereby reducing the costs associated with these adverse events [41]. Therefore, if low-risk patients are appropriately selected for outpatient treatment or early discharge it may significantly decrease the total hospital charges and increase patient safety and satisfaction. Further research should

**Table 2**

Outcome Event Rates after 3 Months of Follow-up.

Outcome	Event Rate %, (95% CI)
Recurrent VTE	1.47% (0.47 to 3.0%)
Fatal PE	0.47% (0.16 to 1.0%)
Major Bleeding	0.81% (0.37 to 1.42%)
Fatal ICH	0.29% (0.06 to 0.68%)
Overall Mortality	1.58% (0.71 to 2.80%)

CI = Confidence Interval, ICH = Intracranial Hemorrhage, PE = Pulmonary Embolism, VTE = Venous Thromboembolism.

**Table 3**

Short-term (&lt;14 days) Outcomes.

Study	Follow up (Days)	N	Mortality (%)	VTE Recurrence (%)	Major Bleeding (%)
Agterof, 2010	10	152	0 (0)	0 (0)	0 (0)
Aujesky, 2011	14	171	0 (0)	0 (0)	2 (1.16)
Davies, 2007	Median of 7 <sup>a</sup>	157	0 (0)	0 (0)	0 (0)
Otero, 2010	10	72	2 (2.8)	1 (1.4)	NA

<sup>a</sup> = This is defined as acute phase of treatment with LMWH, NA = Not available.



**Table 4**  
Short-term (<14 days) Outcome Event Rates.

Outcome	Event Rate %, (95% CI)
Recurrent VTE	0.28% (0.013 to 0.89%)
Major Bleeding	0.46% (0.022 to 1.46%)
Overall Mortality	0.41% (0.006 to 1.46%)

CI = Confidence Interval, VTE = Venous Thromboembolism.

focus on whether the new oral anticoagulants are a safe option for outpatient management of patients with acute PE.

The short-term mortality of PE is reported to be highly variable from <2% in hemodynamically stable patients to more than 95% in patients who experience an arrest [42]. In our subgroup pooled meta-analyses we found that the short-term (<14 days) overall mortality rate for patients selected for outpatient management was low at 0.41% (95% CI: 0.006% to 1.46%). Admittedly, our search strategy only included studies that reported event rates after three months of follow-up and therefore, it is possible that studies reporting short-term but not 3-month outcomes might have been excluded and not included within the pooled event rate. Nonetheless, our reported rate is similar to the short-term (<14 days) rate of mortality of 0.7% (95% CI: 0.3–1.1%) that was previously reported in the literature [43].

A recently published systematic review examined the performance of prognostic risk stratification models in identifying low-risk PE patients for outpatient management [43]. They concluded that the prognostic clinical prediction rules efficiently identify PE patients at low risk of mortality. Clinical gestalt may have potential advantages over clinical prediction rules as it enables clinicians to consider all possible clinical signs, symptoms and diagnostic tests in more details and avoids having to remember or have access to the criteria included within the different risk stratification models. On the other hand, the use of risk stratification models appears more appropriate for use by non-expert physicians, allows to systematically taking into account the most important predictors, is standardized and more reproducible. Five of the 11 included studies in our systematic review utilized a risk stratification method to select patients for outpatient management. In our subgroup analyses we found that although the pooled risk of recurrent VTE was higher in using clinical gestalt versus risk stratification method, these differences did not reach statistical significance. However, heterogeneity was more pronounced in the trials assessing clinical gestalt (high heterogeneity;  $I^2 > 50\%$ ) compared to those assessing different risk stratification methods (moderate heterogeneity;  $I^2 25\text{--}50\%$ ). Hence, future trials assessing if physician's clinical judgment may be equally efficient in selecting patients for outpatient treatment are needed.

Our study has limitations. First, most of our pooled estimates had moderate to high heterogeneity. Sensitivity analyses conducted according to study design (RCTs vs. cohort) or treatment management (outpatient vs. early discharge) did not explain the heterogeneity observed within some of the pooled estimates. This is most likely due to baseline characteristic differences in the component studies. For example, the proportion of cancer patients varied significantly from one study to another from 1% to 22.2% (Table 1). Moreover, higher proportion of patients with malignancy in some of the studies may have influenced the event rates as malignancy is a known risk factor for recurrent VTE, bleeding, and mortality [44]. Second, we combined patients with different VTE treatments (unfractionated heparin, LMWH, vitamin K antagonists) and with different doses. However, these regimens have been shown to have similar efficacy in preventing VTE recurrence and therefore it is unlikely to significantly affect the risk of recurrent events within our analysis [45,46]. Third, the definition of outcome events was not uniform between the studies. Finally, weight estimates are not derived from patient-level longitudinal data. Therefore, the importance of individual risk factors (e.g. prior history of VTE) could not be assessed.

In conclusion, the results of our systematic review and meta-analysis suggest that outpatient management of low-risk patients with acute symptomatic PE is feasible, if home circumstances are adequate, and appears to be safe as measured by low event rates at 14 days and 3 months of follow-up. Future research should focus on the new oral direct anticoagulants for managing patients out of hospital.

### Conflict of Interest

All authors have fulfilled the conditions required for authorship and the authors report no potential conflicts of interest.

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#### Authorship

MC and SP designed the study, performed research, collected, analyzed and interpreted data, performed statistical analysis and wrote the manuscript; GL collected, analyzed, and interpreted data, performed statistical analysis and wrote the manuscript; MR analyzed and interpreted the data, performed statistical analysis and wrote the manuscript; PW, MAR and EG analyzed and interpreted the data and provided vital reviews to the manuscript.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.thromres.2013.08.012>.

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