Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial

Drahomir Aujesky, Pierre-Marie Roy, Franck Verschuren, Marc Righini, Joseph Osterwalder, Michael Egloff, Bertrand Renaud, Peter Verhamme, Roslyn A Stone, Catherine Legall, Olivier Sanchez, Nathan A Pugh, Alfred N'gako, Jacques Cornuz, Olivier Hugli, Hans-Jürg Beer, Arnaud Perrier, Michael J Fine, Donald M Yealy

Summary

Background Although practice guidelines recommend outpatient care for selected, haemodynamically stable patients with pulmonary embolism, most treatment is presently inpatient based. We aimed to assess non-inferiority of outpatient care compared with inpatient care.

Methods We undertook an open-label, randomised non-inferiority trial at 19 emergency departments in Switzerland, France, Belgium, and the USA. We randomly assigned patients with acute, symptomatic pulmonary embolism and a low risk of death (pulmonary embolism severity index risk classes I or II) with a computer-generated randomisation sequence (blocks of 2–4) in a 1:1 ratio to initial outpatient (ie, discharged from hospital ≤24 h after randomisation) or inpatient treatment with subcutaneous enoxaparin (≥5 days) followed by oral anticoagulation (≥90 days). The primary outcome was symptomatic, recurrent venous thromboembolism within 90 days; safety outcomes included major bleeding within 14 or 90 days and mortality within 90 days. We used a non-inferiority margin of 4% for a difference between inpatient and outpatient groups. We included all enrolled patients in the primary analysis, excluding those lost to follow-up. This trial is registered with ClinicalTrials.gov, number NCT00425542.

Findings Between February, 2007, and June, 2010, we enrolled 344 eligible patients. In the primary analysis, one (0·6%) of 171 outpatients developed recurrent venous thromboembolism within 90 days compared with none of 168 inpatients (95% upper confidence limit [UCL] 2·7%; p=0·011). Only one (0·6%) patient in each treatment group died within 90 days (95% UCL 2·1%; p=0·005), and two (1·2%) of 171 outpatients and no inpatients had major bleeding within 14 days (95% UCL 3·6%; p=0·031). By 90 days, three (1·8%) outpatients but no inpatients had developed major bleeding (95% UCL 4·5%; p=0·086). Mean length of stay was 0·5 days (SD 1·0) for outpatients and 3·9 days (SD 3·1) for inpatients.

Interpretation In selected low-risk patients with pulmonary embolism, outpatient care can safely and effectively be used in place of inpatient care.

Funding Swiss National Science Foundation, Programme Hospitalier de Recherche Clinique, and the US National Heart, Lung, and Blood Institute. Sanofi-Aventis provided free drug supply in the participating European centres.

Lancet 2011; 378: 41–48

Published Online June 23, 2011 DOI:10.1016/S0140-6736(11)60824-6

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Bern University Hospital, Bern, Switzerland (Prof D Aujesky MD); **LUNAM University and University of Angers, Angers, France** (Prof P-M Roy MD); **University of Louvain, Brussels, Belgium** (F Verschuren MD); **University of Geneva, Geneva, Switzerland** (M Righini MD, Prof A Perrier MD); **Cantonal Hospital of St Gallen, St Gallen, Switzerland** (J Osterwalder MD); **Cantonal Hospital of Baden, Baden, Switzerland** (M Egloff MD, Prof H-J Beer MD); **University Hospital Henri Mondor, Créteil, France** (B Renaud MD, A N'gako MD); **University of Leuven, Leuven, Belgium** (P Verhamme MD); **VA Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System and The Division of General Internal Medicine, School of Medicine** (Prof M J Fine MD), **Department of Biostatistics** (Prof R A Stone PhD, N A Pugh BS), **and Department of Emergency Medicine** (Prof D M Yealy MD), **University of Pittsburgh, PA, USA; University of Argenteuil, Argenteuil, France** (C Legall MD); **Hôpital Européen Georges Pompidou, Paris, France** (O Sanchez MD); **and University of Lausanne, Lausanne, Switzerland** (Prof J Cornuz MD, O Hugli MD)

Correspondence to: Prof Drahomir Aujesky, Universitätsklinik für Allgemeine Innere Medizin, Inselspital, Bern University Hospital, 3010 Bern, Switzerland **drahomir.aujesky@insel.ch**

Introduction

Outpatient treatment of symptomatic deep vein thrombosis with low-molecular-weight heparin is regarded as usual care.[1–3] Despite practice guideline recommendations to extend outpatient care to selected, haemodynamically stable patients with pulmonary embolism, management of symptomatic pulmonary embolism is predominantly inpatient based.[4–6]

Previous studies of outpatient care after pulmonary embolism were restricted by small sample sizes,[7–12] retrospective designs,[13–15] and the absence of a randomised control group for comparison with inpatient care.[7–18] One randomised trial that compared medical outcomes of patients with pulmonary embolism who were assigned to inpatient versus outpatient care was stopped prematurely because mortality was unacceptably high in both treatment groups.[19] We designed the Outpatient Treatment of Pulmonary Embolism (OTPE) trial to compare the effectiveness, safety, and efficiency of outpatient versus inpatient care for low-risk patients with acute, symptomatic pulmonary embolism as established with a validated clinical prognostic model.[20]

Methods

Study design and participants

We undertook an open-label, randomised, non-inferiority clinical trial at 19 emergency departments in Switzerland, France, Belgium, and the USA. Consecutive adults aged 18 years of age or older with acute, symptomatic, and objectively verified pulmonary embolism who were at low risk of death based on the pulmonary embolism severity index (risk classes I or II; table 1) were eligible to participate.[20] The pulmonary embolism severity index is a clinical prognostic model that was derived and validated in more than 16 000 patients with pulmonary embolism (*C* statistic for overall mortality 0·77–0·87).[20–23] We

defined pulmonary embolism as the acute onset of dyspnoea or chest pain, together with a new contrast filling defect on spiral computed tomography or pulmonary angiography, a new high-probability ventilation-perfusion lung scan, or documentation of a new proximal deep vein thrombosis either by venous ultrasonography or contrast venography.[24,25]

We excluded patients with one or more of the following characteristics: arterial hypoxaemia (oxygen saturation on room air of less than 90% measured by pulse oximetry or a partial pressure of oxygen of less than 60 mm Hg on arterial blood gas analysis), systolic blood pressure of less than 100 mm Hg, chest pain necessitating parenteral opioids, active bleeding, high risk of bleeding defined as stroke during the preceding 10 days, gastrointestinal bleeding during the preceding 14 days or fewer than 75 000 platelets per mm³, severe renal failure (creatinine clearance of <30 mL per min based on the Cockcroft-Gault equation), extreme obesity (body mass >150 kg), history of heparin-induced thrombocytopenia or allergy to heparins, therapeutic oral anticoagulation at the time of diagnosis of pulmonary embolism (international normalised ratio [INR] ≥2·0), any barriers to treatment adherence or follow-up (eg, current alcohol abuse, illicit drug use, psychosis, dementia, or homelessness), pregnancy, imprisonment, diagnosis of pulmonary embolism more than 23 h before the time of screening (to avoid enrolling already stabilised patients), or previous enrolment in the trial.

Participants gave informed written consent. Institutional review boards at all participating sites approved the trial design and informed consent process.

Randomisation and masking

We randomly allocated eligible patients to outpatient treatment or inpatient treatment groups in a one to one ratio at every participating site with a randomised block design generated from a password protected computer web page. To balance recruitment in time and preclude enrolment bias, the blocks varied randomly from two to four patients. Data analysers were unmasked to treatment group assignment.

	Points assigned
Age	+1 per year
Male sex	+10
Cancer*	+30
Heart failure	+10
Chronic lung disease	+10
Pulse ≥110 beats per min	+20
Systolic blood pressure <100 mm Hg	+30
Respiratory rate ≥30 breaths per min	+20
Temperature <36°C	+20
Altered mental status†	+60
Arterial oxygen saturation <90%‡	+20

Overall point score for a patient is obtained by summing the patient's age in years with the points for every applicable predictor. A score of <66 is risk class I, 66–85 is risk class II, 86–105 is risk class III, 106–125 is risk class IV, and >125 is risk class V. *History of cancer or active cancer. †Disorientation, lethargy, stupor, or coma. ‡With or without the administration of supplemental oxygen.

Table 1: **Pulmonary embolism severity index**

Procedures

Patients assigned to outpatient treatment received standardised teaching from a study nurse about self-injection with subcutaneous enoxaparin 1 mg/kg twice every day and were to be discharged from the emergency department within 24 h of randomisation. If self-injection was not possible, a study nurse either taught a caregiver to give the enoxaparin or arranged administration by a visiting nurse. Patients assigned to receive inpatient treatment were admitted to the hospital and received the same enoxaparin regimen. Treating doctors, who were unrelated to the study, autonomously assessed inpatients' readiness for hospital discharge.

In both treatment groups, the study protocol recommended early initiation of oral anticoagulation with vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon, or fluidione) and continuation for a minimum of 90 days. No particular regimen for the initiation of oral anticoagulation was specified. The protocol recommended discontinuation of enoxaparin after 5 or more days of treatment when the INR was 2·0 or more for 2 consecutive days. The patient's primary-care doctor or hospital's anticoagulation clinic personnel managed anticoagulation after discharge from the emergency department or the hospital.

We contacted all patients every day for the week after enrolment, and at 14, 30, 60, and 90 days. We asked patients about symptoms of recurrent venous thromboembolism (VTE; ie, new or worsening dyspnoea, chest pain, or leg pain or swelling), bleeding, and any use of health-care resources. All patients received instructions to report any new symptoms suggestive of VTE or any bleeding episodes to the emergency department.

The primary outcome was the recurrence of symptomatic, objectively confirmed VTE, defined as recurrent pulmonary embolism or new or recurrent deep vein thrombosis within 90 days of randomisation. Diagnostic criteria for recurrent pulmonary embolism were a new intraluminal filling defect on spiral computed tomography or pulmonary angiography, a cutoff of a vessel more than 2·5 mm in diameter on pulmonary angiography, a new perfusion defect involving 75% or more of a lung segment with corresponding normal ventilation (ie, high probability lung scan), or confirmation of a new pulmonary embolism on autopsy.[26] Diagnostic criteria for deep vein thrombosis were the non-compressibility of a new 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.[26]

Secondary clinical outcomes were major bleeding within 14 and 90 days of randomisation and all-cause mortality within 90 days. We defined major bleeding as fatal bleeding, bleeding at critical sites (ie, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or bleeding with a reduction of haemoglobin of 20 g/L or more or resulting in transfusion of two units or more of packed red cells.[27] We used individual endpoints for recurrent VTE, major bleeding, and overall mortality rather than a composite endpoint because these outcomes are likely to arise from distinct mechanisms (eg, pulmonary embolism recurrence *vs* bleeding) and to have a different clinical significance (eg, fatal *vs* non-fatal events).

A committee of three clinical experts from the University Hospital of Lausanne (Switzerland) who were unaware of treatment assignment confirmed all outcomes and classified the cause of all deaths as definitely due to pulmonary embolism, possibly due to pulmonary embolism (eg, sudden death without obvious cause), due to major bleeding, or due to another cause. Final classification was made on the basis of the full consensus of this committee.

We asked all patients to rate their overall satisfaction with care and treatment preferences with an unvalidated 5-point Likert scale questionnaire. Patients completed this questionnaire by telephone 14 days after randomisation; a study nurse asked the questions to patients who were in hospital at follow-up.

We assessed use of major medical resources during 90-day follow-up by counting the overall number of subsequent hospital admissions or outpatient visits to emergency departments or doctors, and home-nursing visits. We classified subsequent hospital admissions or outpatient visits to emergency departments or doctors as potentially related to VTE if a patient had chest or leg symptoms or signs (dyspnoea, chest pain, pleural effusion, or leg pain or swelling), anticoagulation-related complications (bleeding, syncope after an enoxaparin injection, infection at injection site, rise in concentrations of liver enzymes), removal of a vena cava filter, or a medical visit for an anticoagulant refill or injection of an anticoagulant. Two independent data and safety monitoring boards monitored the trial (one in Europe and one in the USA).

Statistical analysis

For the power calculation, we assumed a 90 day recurrence rate of VTE of 0·9% in low-risk inpatients with pulmonary embolism.[28] We postulated that outpatient treatment would be non-inferior to inpatient treatment, specifying a non-inferiority margin of 4%; that is, that the true difference between the rates of recurrent VTE (outpatient rate minus inpatient rate) would not exceed 4%. This non-inferiority margin is equivalent to those used in studies comparing different anticoagulant regimens in acute VTE and outpatient versus inpatient treatment for deep vein thrombosis (3–5%).[1,2,24,29–31] We calculated that 160 patients per treatment group would provide 80% power to detect

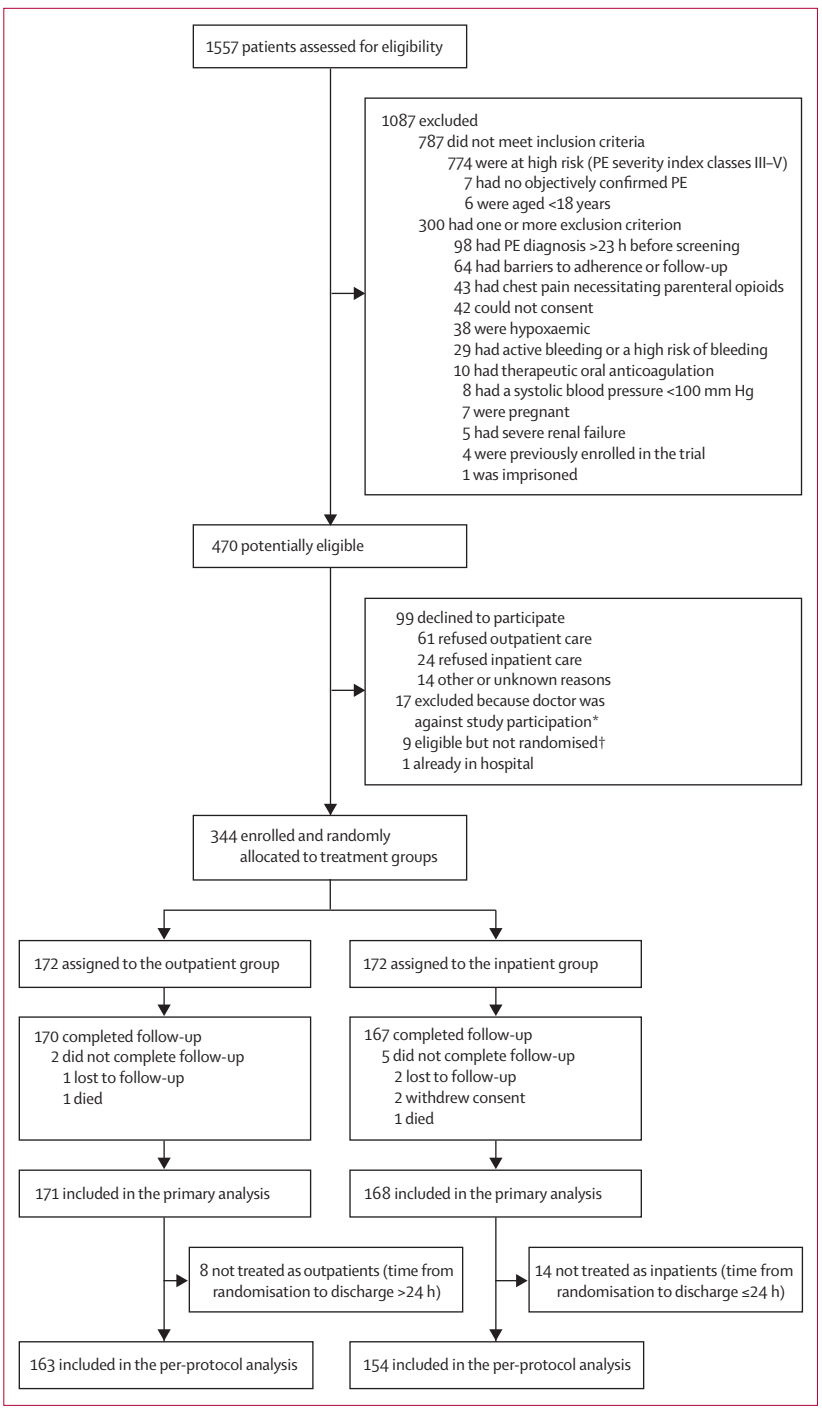

Figure: **Trial profile**
PE=pulmonary embolism. *Doctors did not support study participation because they intended to admit the patient to hospital for testing or treatment of other disorders or for unspecified reasons. †Investigator was either not informed or not available.

	Outpatient group (n=171)	Inpatient group (n=168)
Age (years)	47 (16)	49 (15)
Male sex	84 (49%)	85 (51%)
Race*		
White	129 (75%)	124 (74%)
Black	6 (4%)	6 (4%)
Asian	0	1 (1%)
Unknown	36 (21%)	37 (22%)
Body-mass index (kg/m²)	26·1 (5·0)	26·8 (4·9)
Diagnostic method for index PE		
Spiral computed tomography	152 (89%)	150 (89%)
High-probability lung scanning	13 (8%)	9 (5%)
Pulmonary angiography	0	1 (1%)
Positive test for proximal deep vein thrombosis†	6 (4%)	8 (5%)
Localisation of PE‡		
Central	24 (14%)	16 (10%)
Lobar	60 (35%)	66 (39%)
Segmental	110 (64%)	100 (60%)
Subsegmental	52 (30%)	44 (26%)
Unspecified	29 (17%)	26 (15%)
History of venous thromboembolism	31 (18%)	40 (24%)
Cancer§	1 (1%)	3 (2%)
Bed rest >72 h	14 (8%)	13 (8%)
Surgery within the previous 4 weeks	13 (8%)	12 (7%)
Oestrogen therapy	39 (23%)	34 (20%)
History of thrombophilic condition¶	7 (4%)	6 (4%)
History of heart failure||	2 (1%)	2 (1%)
History of lung disease**	7 (4%)	6 (4%)
Clinical findings		
New or worsening dyspnoea	129 (75%)	126 (75%)
Acute chest pain	121 (71%)	121 (72%)
Haemoptysis	12 (7%)	13 (8%)
Syncope	3 (2%)	5 (3%)
Symptoms of deep vein thrombosis††	51 (30%)	53 (32%)
Systolic blood pressure (mm Hg)	136 (18)	138 (18)
Heart rate (beats per min)	86 (14)	85 (15)
Respiratory rate (breaths per min)	19 (4)	19 (4)
Body temperature (°C)	36·9 (0·6)	36·9 (0·6)
Arterial oxygen saturation (%)‡‡	96 (2)	96 (2)
PE severity index risk score	54 (17)	58 (16)
PE severity index risk class		
I	117 (68%)	109 (65%)
II	54 (32%)	59 (35%)
Creatinine clearance (mL per min)§§	110 (38)	110 (34)

Data are mean (SD) or n (%). PE=pulmonary embolism.*Ascertained by study nurses. †Proximal deep vein thrombosis based on compression ultrasonography or contrast venography in the context of acute dyspnoea or chest pain. ‡More than one localisation was possible. §Active cancer or history of cancer. ¶Activated protein C resistance, factor V Leiden, or G20210A mutation, antiphospholipid antibody syndrome, hyperhomocysteinaemia, or deficiency of protein C, protein S, or antithrombin. ||History of systolic or diastolic heart failure. **History of chronic obstructive pulmonary disease, asthma, or lung fibrosis. ††Unilateral leg pain or swelling. ‡‡With or without supplemental oxygen. §§We estimated creatinine clearance according to the Cockcroft-Gault equation.

Table 2: **Baseline characteristics of patients included in the primary analysis**

a non-inferiority margin of 4% using a one-sided α of 0·05, assuming a 5% drop-out rate.

We compared differences in the percentages of outpatients and inpatients having recurrent VTE with an exact, unconditional permutation test of non-inferiority of outpatient treatment. We used StatXact version 8 for non-inferiority analyses and SAS version 9.2 and Stata version 11 for all other analyses.[32,33] We report an exact 95% upper confidence limit (UCL) for this difference. We obtained this 95% confidence limit by inverting the corresponding one-sided test (ie, identifying all values of the true difference that would not be rejected by the corresponding one-sided test). Because of the presence of an unknown quantity (the true rate in the control group), this approach provides a conservative upper bound for how large the true difference is likely to be. We used the same non-inferiority approach to compare major bleeding and death. The expected small number of events precluded any adjustment for study site.

We interpolated INR values in time, and compared the percentage of time spent in each INR category using multinomial regression, adjusting for clustering at the patient level.[34] We compared quantitative measures of resource use between intervention groups with negative binomial regression with a bootstrap variance estimator. We also did a per-protocol analysis of the medical outcomes, excluding outpatients discharged more than 24 h after randomisation and inpatients discharged 24 h or less after randomisation.[35] This trial is registered with ClinicalTrials.gov, number NCT00425542.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. DA, RAS, MJF, and DMY had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between February, 2007, and June, 2010, we randomly allocated 172 eligible patients to the outpatient group and 172 to the inpatient group (figure; table 2). One outpatient and two inpatients were lost to follow-up and two inpatients withdrew consent during follow-up; therefore, we included 171 outpatients and 168 inpatients in the primary analysis.

Time from presentation to the emergency department until randomisation was much the same for outpatients and inpatients (13·9 h *vs* 13·3 h; p=0·24). Duration of treatment with low-molecular-weight heparin was longer for patients in the outpatient group than it was for patients in the inpatient group (table 3). 128 (75%) of 170 outpatients self-administered injections (information about administration status was not available for one patient). The percentage of time spent in the therapeutic INR range (defined as 2·0–3·0) was around 52% in both groups (table 3).

In the primary-analysis population, one (0·6%) of 171 outpatients and no inpatients had a recurrent VTE within 90 days (table 4), meeting our criterion for non-inferiority (p=0·011; exact 95% UCL for difference 2·7%). This UCL suggests that the true outpatient event rate is not likely to exceed the true inpatient event rate by more than 2·7%. The one VTE occurred in a woman with cervical cancer who initially had bilateral segmental pulmonary embolism. Despite continued anticoagulation with enoxaparin, she was diagnosed with symptomatic, subsegmental pulmonary embolism on day 83. The per-protocol analysis also supported non-inferiority for recurrent VTE (p=0·014; exact 95% UCL for difference 2·9%).

In the primary-analysis population, two outpatients and no inpatients had major bleeding within 14 days, suggesting non-inferiority (table 4). The major bleeds were intramuscular haematomas occurring on days 3 and 13 (one patient had insertion of a vena cava filter). Because one additional outpatient developed major bleeding within 90 days (menometrorrhagia on day 50), we slightly exceeded our non-inferiority threshold (table 4). However, only two events occurred in outpatients in the per-protocol population by 90 days, supporting non-inferiority (table 4).

One patient in each treatment group died within 90 days in the primary-analysis population (table 4),

	Outpatient group	Inpatient group	p value
Duration of treatment with low-molecular-weight heparin (days)*	11·5 (12·8)	8·9 (10·1)	0·04
Time from diagnosis of PE to start of oral anticoagulation (h)†	16 (5–23)	8 (3–22)	0·08
Oral anticoagulation managed by primary-care doctor‡	122/167 (73%)	117/157 (75%)	0·80
Percentage of time spent in INR categories§			0·49
INR category <2·0	34·7%	32·0%	..
INR category 2·0–3·0	51·8%	52·5%	..
INR category >3·0	13·5%	15·6%	..
Received anticoagulation for ≥90 days¶	170/170 (100%)	163/165 (99%)	0·24

Data are mean (SD), median (IQR), or n/N (%), unless otherwise stated. PE=pulmonary embolism. INR=international normalised ratio. *Duration of treatment was missing for nine outpatients and 11 inpatients; three outpatients and one inpatient received low-molecular-weight heparin throughout follow-up. †Excludes three outpatients and two inpatients with missing data, and eight outpatients and eight inpatients who were receiving oral anticoagulation before diagnosis. ‡Four outpatients and 11 inpatients had no INR values recorded. §Calculated with linear interpolated INR values. ¶Excludes two deaths and two inpatients with missing data.

Table 3: **Treatment characteristics**

	Outpatient group	Inpatient group	Difference in percentages ($\%_{outpatient}-\%_{inpatient}$)	Upper 95% CL for difference	p value*
Primary analysis outcomes within 90 days†					
Recurrent VTE	1 (0·6%)‡	0	0·6%	2·7%	0·011
Major bleeding	3 (1·8%)	0	1·8%	4·5%	0·086
Intramuscular	2 (1·2%)	0	1·2%	3·6%	0·031
Menometrorrhagia	1 (0·6%)	0	0·6%	2·7%	0·011
Overall mortality	1 (0·6%)§	1 (0·6%)¶	0%	2·1%	0·005
Primary analysis outcomes within 14 days†					
Recurrent VTE	0	0	0%	1·7%	0·003
Major bleeding	2 (1·2%)	0	1·2%	3·6%	0·031
Intramuscular	2 (1·2%)	0	1·2%	3·6%	0·031
Menometrorrhagia	0	0	0%	1·7%	0·003
Overall mortality	0	0	0%	1·7%	0·003
Per-protocol outcomes within 90 days‖					
Recurrent VTE	1 (0·6%)‡	0	0·6%	2·9%	0·014
Major bleeding	2 (1·2%)	0	1·2%	3·8%	0·040
Intramuscular	2 (1·2%)	0	1·2%	3·8%	0·040
Menometrorrhagia	0	0	0%	1·8%	0·004
Overall mortality	1 (0·6%)§	1 (0·6%)¶	0%	2·1%	0·007

CL=confidence limit. VTE=venous thromboembolism. *One-sided exact p value for non-inferiority; specified non-inferiority margin of 4%. †171 patients in the outpatient group and 168 patients in the inpatient group. ‡Patient had non-fatal pulmonary embolism. §Patient died from accident-related trauma with resultant aortic rupture. ¶Patient died from pneumonia and lung cancer. ‖163 patients in the outpatient group and 154 patients in the inpatient group.

Table 4: **Effectiveness and safety outcomes**

	Outpatient group (n=171)	Inpatient group (n=168)	p value
Length of initial hospital stay (days)*	0·5 (1·0)	3·9 (3·1)	N/A
Treated entirely in the outpatient setting†	163 (95%)	14 (8%)	<0·0001
Hospital readmissions within 90 days			
All	18	23	0·60
Potentially venous thromboembolism-related‡	11	6	0·58
Emergency department visits within 90 days			
All	36	36	0·94
Potentially venous thromboembolism-related‡	27	19	0·51
Visits to a primary-care doctor within 90 days			
All	202	216	0·67
Potentially venous thromboembolism-related‡	112	92	0·58
Home nursing visits for enoxaparin injection within 90 days	348	105	0·53§

Data are mean (SD), n (%), or n. *Time from randomisation to discharge; we did not calculate a p value because these groups are expected to differ by definition. †Time interval of ≤24 h between randomisation and discharge. ‡Related to chest or leg symptoms or signs (dyspnoea, chest pain, pleural effusion, leg swelling, or leg pain), anticoagulation-related complications (bleeding, syncope after injection, infection at injection site, or raised concentrations of liver enzymes), removal of a vena cava filter, or a care visit for medication refill or injection of enoxaparin. Much the same number of outpatients and inpatients were assessed for suspected recurrent venous thromboembolism (60 outpatients *vs* 46 inpatients; p=0·42). §This p value is unexpectedly large because the bootstrap distribution of total home nursing visits is quite variable due to a few extreme values in each treatment group.

Table 5: **Medical resources used by treatment group**

Panel: Research in context

Systematic review

We searched the PubMed database without language or date restrictions with the search terms "pulmonary embolism", "ambulatory", "outpatient", and "home". We also hand-searched conference abstracts from the International Society on Thrombosis and Haemostasis and the American Society of Hematology from 2007 to 2010. We reviewed randomised-controlled trials, prospective and retrospective studies, and case-series, without explicit critical appraisal. Previous non-randomised studies showed that outpatient care of carefully selected, haemodynamically stable patients with pulmonary embolism might be effective and safe.[7–18,36,37] One randomised trial[19] that tried to compare medical outcomes of patients with pulmonary embolism who were assigned to inpatient versus outpatient care was stopped prematurely because mortality was unacceptably high in both treatment groups.

Interpretation

Our trial is the only randomised trial so far that compares the effectiveness, safety, and efficiency of outpatient versus inpatient care of patients with acute, symptomatic pulmonary embolism. We show that, in selected low-risk patients (identified with the pulmonary embolism severity index; table 1), outpatient treatment with low-molecular-weight heparin does not differ from inpatient treatment in terms of effectiveness, safety, and acceptance by patients, but reduces time spent in hospital.

supporting non-inferiority of outpatient treatment for overall mortality. The outpatient died immediately from trauma-related aortic rupture on day 34, and the inpatient died from pneumonia and cancer on day 17.

337 (99%) of 339 patients completed the satisfaction questionnaire at 14 days after randomisation. Overall, 156 (92%) of 170 outpatients and 158 (95%) of 167 inpatients were very satisfied or satisfied with the medical care received (p=0·39). 23 (14%) of 170 outpatients would have preferred to be treated for longer than they were in hospital, and 49 (29%) of 167 inpatients would have preferred to be treated at home initially rather than in the hospital.

After randomisation, the mean time initially spent in the hospital for patients assigned to outpatient treatment was 0·5 days (SD 1·0) compared with 3·9 days (3·1) for patients assigned to inpatient treatment (table 5). Patients in both groups had much the same numbers of hospital readmissions, emergency department visits, and outpatient visits to a doctor's office within 90 days (table 5). Potential VTE-related medical resource use was much the same between groups, although outpatients had non-significantly more home-nursing visits for enoxaparin injections than did inpatients (348 *vs* 105; p=0·53); these counts were very variable due to usage outliers and the fact that only 24 (14%) of 171 outpatients and six (4%) of 168 inpatients received home-nursing visits (p<0·001).

Discussion

Our multicentre trial of low-risk patients with acute, symptomatic pulmonary embolism showed that outpatient treatment with low-molecular-weight heparin is not inferior to inpatient treatment in terms of effectiveness and safety. Our findings are consistent with previous non-randomised studies and systematic reviews showing that outpatient care of pulmonary embolism is associated with low rates of recurrent VTE (0–6·2%), major bleeding (0–2·3%), and death (0–5·0%; panel).[8,9,11–18,36,37] Although we showed non-inferiority for outpatient treatment with respect to major bleeding at 14 days, we did not achieve non-inferiority at 90 days because of an additional bleeding episode that occurred 50 days after randomisation. However, given this time latency, it is unlikely that this bleeding event was related to randomisation to outpatient treatment.

Our findings support a shift in clinical management of pulmonary embolism for a substantial proportion of low-risk patients to the outpatient setting. Of 1557 patients screened in our study, 470 (30%) met our eligibility criteria and 344 (73%) of those eligible were enrolled. Because of some of the reasons for exclusion (eg, diagnosis of pulmonary embolism >23 h before time of screening), the proportion of patients who are candidates for outpatient treatment might be higher. Dependent on the criteria used to identify low-risk patients, the proportion of enrolled patients varied from 13% to 51% in previous prospective studies of outpatient care for pulmonary embolism.[8,9,16,18,19] Outpatient treatment protocols for pulmonary embolism and follow-up in outpatient thrombosis units have the potential to further increase the proportion of low-risk patients who are managed at home.[14,15]

Compared with inpatient care, patients in the outpatient group had a 3·4-day reduction in mean length of initial hospital stay, with much the same rates of hospital

readmission, emergency department visits, and outpatient visits to doctors as did the inpatient group. Our findings suggest that cost savings from reductions in hospital stay might be partially offset by an increased frequency of home-nursing visits for outpatients.

The duration of treatment with low-molecular-weight heparin was 2·6 days longer for outpatients than it was for inpatients. These results are consistent with a previous study showing that patients with pulmonary embolism who were discharged from hospital early had less intensive anticoagulant monitoring, a longer time to achieve a therapeutic INR, and a longer overlap of low-molecular-weight heparin and oral anticoagulation than did inpatients.[38]

We also show that outpatient care was well accepted by patients. Patients who were treated as outpatients had equally high satisfaction with care as did inpatients. Our findings are consistent with previous studies showing that patients with pulmonary embolism prefer outpatient treatment and are very satisfied with management at home.[17,18]

We used the pulmonary embolism severity index, which is an accurate and reliable clinical prognostic model, to identify low-risk patients with pulmonary embolism,[20,23] suggesting that doctors do not have to rely on markers of myocardial dysfunction or injury (eg, brain natriuretic peptide, troponin, or echocardiographic measurements of right ventricular function) to safely identify candidates for outpatient care. Moreover, 24 patients who had central pulmonary embolism on computed tomography were safely treated as outpatients in our study, suggesting that central pulmonary embolism might not be an absolute indication for hospitalisation. A previous trial[19] that randomly allocated patients with pulmonary embolism to outpatient versus inpatient care by use of a non-validated prognostic model to identify low-risk patients was stopped prematurely because mortality was unacceptably high in both treatment groups, suggesting that only validated risk stratification methods should be used to select those patients at low risk who might benefit from outpatient care.

Our study has potential limitations. First, because age and history of cancer have a high prognostic weight in the pulmonary embolism severity index, the patients enrolled in our study were relatively young and had a low prevalence of cancer.[20] Age of 70 years or older and cancer are known risk factors for complications in patients with pulmonary embolism, and caution must be applied when treating such patients at home.[39,40] Second, we used enoxaparin twice per day for the initial treatment of pulmonary embolism. Straightforward, similarly effective treatment regimens, such as low-molecular-weight heparins or fondaparinux injected once per day or oral direct thrombin or factor Xa inhibitors,[41–43] might further aid outpatient care of VTE and decrease the need for home nursing visits. Third, our study was open-label, which could bias medical care and assessments of study outcomes. However, we mitigated this by enrolling patients consecutively, objectively assessing medical outcomes, and adjudicating outcomes with a committee masked to treatment status. Finally, 17 patients were not randomly allocated to intervention groups because their treating doctors declined participation. Given this exclusion occurred prior to randomisation and in a small number of patients, the risk of selection bias and outcomes distortion was probably low.

Thus, in selected low-risk patients identified by use of the pulmonary embolism severity index, outpatient treatment with low-molecular-weight heparin is feasible in a substantial proportion of patients with pulmonary embolism. Outpatient treatment is not inferior to inpatient treatment in terms of efficacy and safety, is well accepted by patients, and reduces time spent in hospital.

Contributors

A steering committee of four academic investigators (DA, RAS, MJF, and DMY) designed the study, analysed and interpreted the data, and wrote the first draft of the report. All authors revised and reviewed the report. DA, PMR, FV, MR, JO, ME, BR, PV, CL, OS, AN, OH, and DMY were involved in data collection. NAP and RAS did all statistical analyses.

Conflicts of interest

DA has received honoraria from Sanofi-Aventis and Bayer. PMR has received grants, honoraria, consultancy fees, and payments from GlaxoSmithKline, Sanofi-Aventis, Bayer, Biomérieux, Boehringer Ingelheim, Eli Lilly, and LFB Biomédicaments. PV has received grants, consultancy fees, and payments from Sanofi-Aventis, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, ThromboGenics, Leo, and Pfizer. OH has received grants from Pfizer and MSD. HJB has received honoraria from Sanofi-Aventis, Bayer, Boehringer Ingelheim, Menarini, and GlaxoSmithKline.

Acknowledgments

This study was supported by grants from the Swiss National Science Foundation (3200B0-1121), the Programme Hospitalier de Recherche Clinique 2007 (21-03), and the US National Heart, Lung, and Blood Institute (1R01HL085565-01A2). Sanofi-Aventis provided free drug supply in the participating European centres. We thank Emmanuelle Le Moigne (Brest, France), David Elkharrat (Boulogne, France), Dominique Elkouri (Nantes, France), Mark Courtney (Chicago, IL, USA), Didier Honnart (Dijon, France), Jeannot Schmidt (Clermont-Ferrand, France), Jeffrey Kline (Charlotte, NC, USA), Yves Poitrineau (Thiers, France), and Bertrand Yersin (Lausanne, Switzerland).

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