Randomised controlled trial of a prognostic assessment and management pathway to reduce the length of hospital stay in normotensive patients with acute pulmonary embolism

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The use of a prognostic assessment and management pathway reduces the length of hospital stay for normotensive patients with acute pulmonary embolism https://bit.ly/3gYGHWE

Cite this article as: Jiménez D, Rodríguez C, León F, *et al*. Randomised controlled trial of a prognostic assessment and management pathway to reduce the length of hospital stay in normotensive patients with acute pulmonary embolism. *Eur Respir J* 2022; 59: 2100412 [DOI: 10.1183/13993003.00412-2021].

Received: 11 Feb 2021
Accepted: 18 June 2021

Abstract

Background The length of hospital stay (LOS) for acute pulmonary embolism (PE) varies considerably. Whether the upfront use of a PE prognostic assessment and management pathway is effective in reducing the LOS remains unknown.

Methods We conducted a randomised controlled trial of adults hospitalised for acute PE: patients were assigned either to a prognostic assessment and management pathway involving risk stratification followed by predefined criteria for mobilisation and discharge (intervention group) or to usual care (control group). The primary end-point was LOS. The secondary end-points were the cost of prognostic tests and of hospitalisation, and 30-day clinical outcomes.

Results Of 500 patients who underwent randomisation, 498 were included in the modified intention-to-treat analysis. The median LOS was 4.0 days (interquartile range (IQR) 3.7–4.2 days) in the intervention group and 6.1 days (IQR 5.7–6.5 days) in the control group (p<0.001). The mean total cost of prognostic tests was EUR 174.76 in the intervention group, compared with EUR 233.12 in the control group (mean difference EUR −58.37, 95% CI EUR −84.34 to −32.40). The mean total hospitalisation cost per patient was EUR 2085.66 in the intervention group, compared with EUR 3232.97 in the control group (mean difference EUR −1147.31, 95% CI EUR −1414.97 to −879.65). No significant differences were observed in 30-day readmission (4.0% *versus* 4.8%), all-cause mortality (2.4% *versus* 2.0%) or PE-related mortality (0.8% *versus* 1.2%) rates.

Conclusions The use of a prognostic assessment and management pathway was effective in reducing the LOS for acute PE.

Introduction

Pulmonary embolism (PE) remains a worldwide major health issue [1, 2]. In addition to the immense impact of venous thromboembolism (VTE) on morbidity and mortality, the economic burden of the disease is considerable, costing the healthcare system in the USA more than USD 1.5 billion/year [3], with much of this enormous expense related to the period of hospital stay [4–7]. A study that included patients hospitalised at Brigham and Women's Hospital from September 2003 to May 2010 estimated that the mean total hospitalisation cost for a patient with PE was USD 8764 [4]. Further, there is emerging concern about hospital-acquired diseases and morbid illness that complicate the duration of hospital stay. Despite the recent trends indicating a decline in length of hospital stay (LOS) after PE diagnosis [8], the duration of hospitalisation is still inexplicably high [9]. Therefore, validating strategies aimed at safely reducing the LOS is of paramount importance.

Given that the key to effective triage and treatment of acute PE lies in timely assessment of the prognosis, timely risk stratification might contribute to reduce LOS [10]. For unstable patients with PE, guidelines generally recommend aggressive treatment in an intensive care unit [11–13]. Among patients without hypotension, those deemed as having a low risk for early complications might benefit from an abbreviated hospital stay or outpatient management, whereas others might benefit from close observation, and consideration of advanced therapies in case of clinical deterioration [14].

No randomised trials have assessed the effect of early prognostication and subsequent management on the LOS and the outcomes of patients with acute PE. Therefore, we designed a multicentre randomised controlled trial to test the hypothesis that a management strategy guided by early use of a prognostic pathway would be more effective than usual care in reducing LOS in hospitalised patients with acute PE.

Methods

Trial design and oversight

From April 15, 2016, to December 15, 2019, we conducted a multicentre randomised open-label trial comparing a prognostic assessment and management pathway including risk stratification followed by predefined criteria for mobilisation and hospital discharge (intervention group) *versus* usual care (control group) among outpatients hospitalised with acute PE. The institutional review board at each of the participating sites approved the protocol, which is available in the supplementary appendix. The study has been registered at ClinicalTrials.gov (NCT02733198). The authors designed the trial, collected the data and performed the analyses. The funders had no role in the conception, design or conduct of the trial, nor did their representatives participate in the collection, management, analysis, interpretation or presentation of the data or in the preparation, review or approval of the manuscript. All the authors revised the manuscript, vouch for the accuracy and completeness of the data and approved the decision to submit the manuscript for publication.

Trial sites and patient population

The trial was conducted in nine academic hospitals across Spain. Adults (age $\geqslant$18 years) who required hospitalisation for objectively diagnosed, acute symptomatic PE were eligible. Patients were excluded if they were pregnant or if they had haemodynamic instability or an indication for reperfusion therapies at the time of PE diagnosis. Complete lists of inclusion and exclusion criteria are provided in the supplementary appendix.

Randomisation

Investigators randomised eligible patients by a centralised, web-based system in a 1:1 ratio to either the intervention group or control group, in permuted blocks of four and six, stratified according to trial site. Given the nature of the intervention, clinicians and research personnel were aware of trial-group assignments after randomisation.

Trial interventions

Per protocol, intervention for patients in the active arm was provided by trial investigators who were strictly advised to follow the protocol-recommended pathway, while management of patients in the control arm was performed by other clinicians according to their routine practice. The prognostic assessment and management pathway used in the intervention arm consisted of 1) PE risk stratification, followed by predefined recommended criteria for 2) mobilisation and 3) hospital discharge (supplementary appendix).

Patients in the intervention arm had to be risk stratified. Within 6 h of randomisation, trial investigators measured vital signs (*i.e.* heart rate, systolic blood pressure and oxygen saturation) to calculate the simplified Pulmonary Embolism Severity Index (sPESI) [15]. A sPESI score of 0 identified low-risk

patients. Patients with a sPESI ⩾1 constituted an intermediate-risk group. Within this group, patients had to undergo troponin testing and, for those with a positive result, echocardiographic assessment for right ventricular (RV) dysfunction. Patients with a sPESI ⩾1 and abnormality for only troponin levels or only echocardiographic RV dysfunction (or neither) comprised the intermediate-low-risk group. In turn, patients with a sPESI ⩾1 and both elevated troponin levels and echocardiographic RV dysfunction comprised the intermediate-high-risk group (supplementary table S1).

Mobilisation was defined as ambulation for at least 20 min/day. The trial protocol requested immediate (*i.e.* the first morning after randomisation) mobilisation for low-risk patients. Intermediate-low-risk patients were encouraged for early mobilisation (from the second morning after randomisation) when they met the following criteria: systolic blood pressure >100 mmHg, heart rate <100 beats/min and pulse oximetry >90% without supplemental oxygen. Intermediate-high-risk patients required bed rest and close observation for the first 48 h after randomisation. If there was no clinical deterioration within the first 48 h, then they were managed the same way as intermediate-low-risk patients.

Predefined criteria for discharge were meeting criteria for mobilisation, adequate vital signs (systolic blood pressure >100 mmHg, heart rate <100 beats/min and pulse oximetry >90%) and absence of pain requiring intravenous analgesia. A printed checklist detailing the prognostic assessment and management pathway was added to the medical paper charts of patients assigned to the intervention arm to remind attending physicians of the necessity of risk stratification, and the criteria for mobilisation and hospital discharge.

Patients randomly assigned to usual care were treated according to the practices of individual care team practices.

End-points

The primary end-point of the trial was the LOS, defined as the interval from diagnosis of PE at the emergency department to discharge from the hospital. Secondary end-points included the cost of prognostic tests and of hospitalisation, 30-day event rates for readmissions, all-cause and PE-related mortality, and serious adverse events. Death was attributed to PE if there was no other explanation or there was autopsy or radiological confirmation of PE. We also assessed the patient satisfaction with the care received for acute PE. Surviving patients rated their satisfaction in response to the question "How would you rate your overall care for this episode of PE?" Responses were recorded on a visual scale of 0 to 100, from "very unsatisfactory" to "very satisfactory". Patients were considered satisfied if the response recorded was 80–100. A list of the pre-specified secondary end-points and the criteria for adjudication of all the end-points are provided in the supplementary appendix. A committee of clinicians from Ramon y Cajal Hospital (Spain) who were unaware of the study group assignments adjudicated all the suspected events and causes of death.

Statistical analysis

For the primary end-point, a two-sided hypothesis with a p-value <0.05 was considered to indicate statistical significance. All other hypothesis tests were two-tailed and considered exploratory. The primary analyses were performed in the modified intention-to-treat population, which included all patients who were randomly assigned to the intervention group and received appropriate risk stratification (*i.e.* according to the trial protocol). Comparisons were made using the t-test, the Mann–Whitney U test, Fisher's exact test or the chi-squared test, as appropriate. The trial was designed to enrol 250 patients in each group. Allowing for a loss to follow-up of 10%, this number provided the study with a power of 80% to detect a reduction in the time to discharge from 6.0 to 4.0 days with the use of the prognostic assessment and management pathway. Assumptions included the use of a two-tailed test, a 5% type I error rate and an SD of 7.5 days in LOS in both groups. The statistical analyses were performed using the SPSS software package (version 26.0, IBM Corp.) and Stata (version 16.1, StataCorp LLC).

Results

Patients

From April 15, 2016, to December 15, 2019, a total of 679 patients underwent screening, 500 patients underwent randomisation and 498 were included in the modified intention-to-treat analysis: 249 patients were assigned to the intervention group and 249 to the control group (figure 1). The mean age was 66 years and <50% of the patients were women. The characteristics of the patients at baseline did not differ significantly between the two trial groups (table 1).

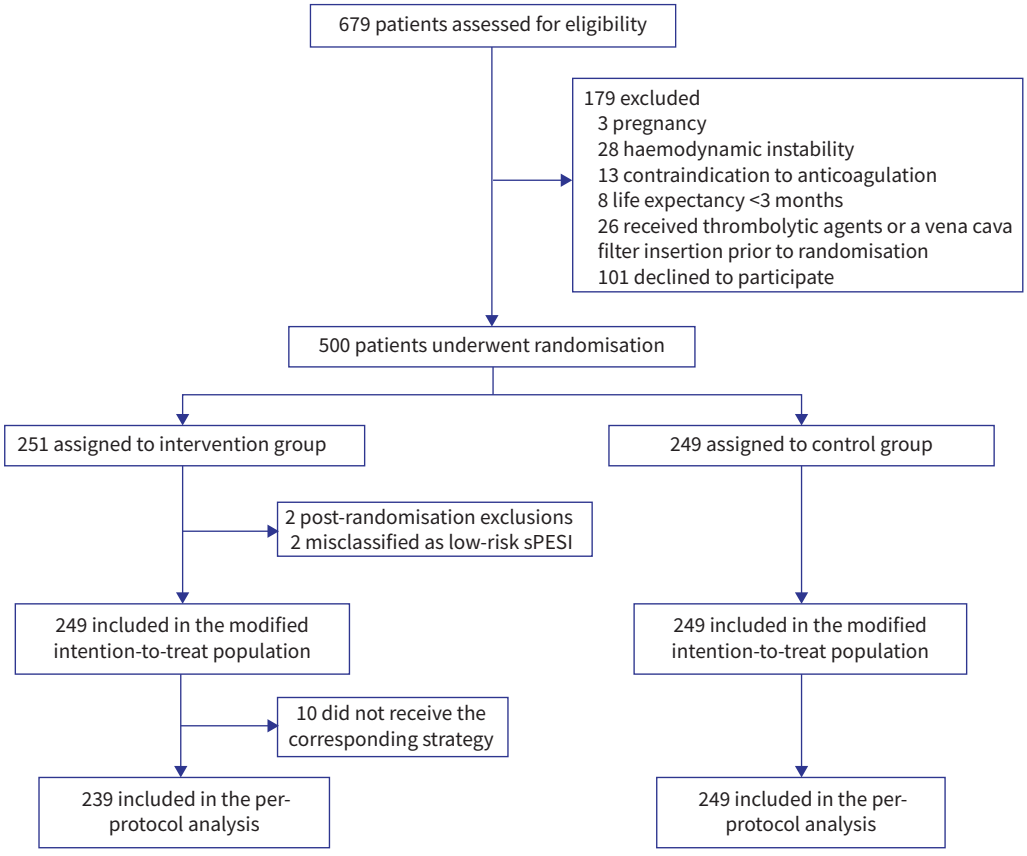

FIGURE 1 Flowchart of the trial. sPESI: simplified Pulmonary Embolism Severity Index.

Intervention

Of the 249 patients assigned to the intervention group, 24% were classified as low risk, 64% as intermediate-low risk and 12% as intermediate-high risk.

The median time from randomisation to the initiation of mobilisation was 2.0 days (interquartile range (IQR) 1.5–2.0 days) in the intervention group and 2.0 days (IQR 2.0–2.0 days) in the usual care group ($p<0.01$). In the intervention group, the median time from randomisation to the initiation of mobilisation was 1.0 day in the low-risk group, 2.0 days in the intermediate-low-risk group and 2.0 days in the intermediate-high-risk group. Immediate mobilisation was not performed in four patients in the low-risk intervention group who were thought to be too ill to be mobilised. Six patients in the intermediate-low-risk group were mobilised on the first morning after randomisation.

End-points

Table 2 summarises the outcomes for study patients. In the modified intention-to-treat analysis, the median LOS was 4.0 days in the intervention group *versus* 6.1 days in the usual care group ($p<0.001$) (figure 2). For patients randomised to the intervention group, the median LOS was 2.0 days (IQR 1.0–3.0 days) in the low-risk category, 4.0 days (IQR 3.0–5.0 days) in intermediate-low-risk category and 5.0 days (IQR 4.0–6.0 days) in the intermediate-high-risk category (supplementary table S2). Assignment to the prognostic assessment and management pathway significantly reduced the use of prognostic tests: 88% in the intervention group (95% CI 83.3–91.7%) compared with 99% (95% CI 95.4–99.3%) in the control group (table 3). This difference translated into a significant difference in the mean total cost of prognostic tests: EUR 174.76 in the intervention group compared with EUR 233.12 in the control group (mean difference EUR −58.37, 95% CI EUR −84.34 to −32.40). The mean total hospitalisation cost per patient was EUR 2085.66 in the intervention group, compared with EUR 3232.97 in the control group (mean difference EUR −1147.31, 95% CI EUR −1414.97 to −879.65).

30-day follow-up data were available for all patients. All-cause readmission rates were similarly low in both groups (table 2). 30-day all-cause (2.4% *versus* 2.0%, relative risk 1.21, 95% CI 0.36–4.00) and

TABLE 1 Baseline characteristics of the patients

Characteristic	Intervention group	Control group
Subjects, n	249	249
Age, years		
Mean (95% CI)	66.0 (64.0–68.1)	65.4 (63.3–67.5)
Range	19–92	18–92
Sex, n (%)		
Male	126 (51)	128 (51)
Female	123 (49)	121 (49)
Medical history, n (%)		
Previous VTE	41 (16)	31 (12)
Cancer[#]	48 (19)	50 (20)
Recent surgery[¶]	31 (12)	34 (14)
Immobilisation[+]	40 (16)	30 (12)
Chronic lung disease	36 (15)	29 (12)
Congestive heart failure	22 (9)	23 (9)
Recent major bleeding	1 (0.4)	2 (0.8)
Symptoms, n (%)		
Dyspnoea	199 (80)	207 (83)
Chest pain	123 (50)	121 (49)
Haemoptysis	17 (7)	17 (7)
Syncope	34 (14)	36 (15)
Systolic blood pressure, mmHg		
Mean (95% CI)	136.9 (134.3–139.5)	137.2 (134.5–139.9)
Heart rate, beats/min		
Mean (95% CI)	92.5 (90.1–94.9)	93.7 (91.2–96.1)
Arterial oxyhaemoglobin saturation, %		
Mean (95% CI)	91.9 (91.1–92.8)	92.8 (91.9–93.7)
sPESI[§], n (%)		
Low risk	88 (35)[f]	83 (33)
High risk	161 (65)	166 (67)
Risk stratum, n (%)		
Low-risk	60 (24)	-
Intermediate-low risk	159 (64)	-
Intermediate-high risk	30 (12)	-
Haemoglobin, g·dL^{-1}		
Mean (95% CI)	13.6 (13.4–13.9)	13.6 (13.4–13.9)
Serum creatinine, mg·dL^{-1}		
Mean (95% CI)	1.0 (0.9–1.0)	1.0 (0.9–1.0)
Medications for the acute episode, n (%)		
Low-molecular-weight heparins	247 (99)	242 (97)
Unfractionated heparin	1 (0.4)	3 (1.2)
Fondaparinux	0	1 (0.4)
Direct oral anticoagulants	1 (0.4)	3 (1.2)

VTE: venous thromboembolism; sPESI: simplified Pulmonary Embolism Severity Index. [#]: active or under treatment in the last year; [¶]: in the previous month; [+]: immobilised patients defined as non-surgical patients who had been immobilised (*i.e.* total bed rest with bathroom privileges) for ⩾4 days in the month prior to PE diagnosis; [§]: calculation of the sPESI was not mandatory in the control arm (the table reflects calculated sPESI by the study authors (not treating physicians)); [f]: 28 patients had additional tests ordered in the emergency department that qualified them as intermediate risk.

PE-related mortality (0.8% *versus* 1.2%, relative risk 0.66, 95% CI 0.11–4.01) were not significantly different in the intervention and control groups. Supplementary table S3 summarises the reasons for readmission and the causes of death.

For the analysis of patients' satisfaction, data were available for 147 of 249 patients in the intervention group and for 152 of 249 patients in the control group. No difference was found between groups in the number of patients expressing satisfaction: intervention group 45 of 147 (30.6%, 95% CI 23.3–38.7%) *versus* usual care group 54 of 152 (35.5%, 95% CI 27.9–43.7%).

TABLE 2 End-points

Outcomes	Intervention group	Control group	Difference or relative risk (95% CI)[#]
Subjects, n	249	249	
Length of hospital stay, days			−2.1 (−2.6 to −1.7)
Median (IQR)	4.0 (3.7–4.2)	6.1 (5.7–6.5)	
Cost of prognostic tests, EUR			−58.37 (−84.34 to −32.40)
Mean (95% CI)	174.76 (155.99–193.52)	233.12 (215.08–251.17)	
Cost of hospitalisation, EUR			−1147.31 (−1414.97 to −879.65)
Mean (95% CI)	2085.66 (1947.75–2223.58)	3232.97 (3002.81–3463.13)	
30-day readmission rate, n (%)	10 (4.0)	12 (4.8)	0.83 (0.35–1.95)
30-day all-cause mortality, n (%)	6 (2.4)	5 (2.0)	1.21 (0.36–4.00)
30-day PE-related mortality, n (%)	2 (0.8)	3 (1.2)	0.66 (0.11–4.01)
30-day serious adverse events, n (%)	10 (4.0)	7 (2.8)	1.45 (0.54–3.86)
Fatal recurrence	1 (0.4)	1 (0.4)	
Fatal bleeding	1 (0.4)	1 (0.4)	
Non-fatal recurrence	2 (0.8)	0	
Non-fatal major bleeding	2 (0.8)	1 (0.4)	
Haemodynamic collapse	2 (0.8)	4 (1.6)	
Others[¶]	2 (0.8)	0	

IQR: interquartile range; PE: pulmonary embolism. [#]: difference (intervention–control) is shown for means and relative risk (intervention:control) is shown for percentages; [¶]: purpura and pneumonia.

Sensitivity analysis and subgroups

The results with respect to the intervention effect were consistent in analyses of the per-protocol cohort (supplementary table S4). Further, findings were similar across the predefined subgroups (supplementary figure S1).

Discussion

This randomised controlled trial examined the effect of a prognostic assessment and management pathway in normotensive patients with acute PE. We found that the intervention, which included prognostication and use of objective criteria for mobilisation and early hospital discharge, was safe and associated with a reduction in downstream laboratory or echocardiographic testing. It was also effective in reducing LOS by 2 days, compared with usual care. These changes resulted in a net reduction in the mean hospitalisation costs. Results were consistent across the study subgroups and in per-protocol analyses. These findings may

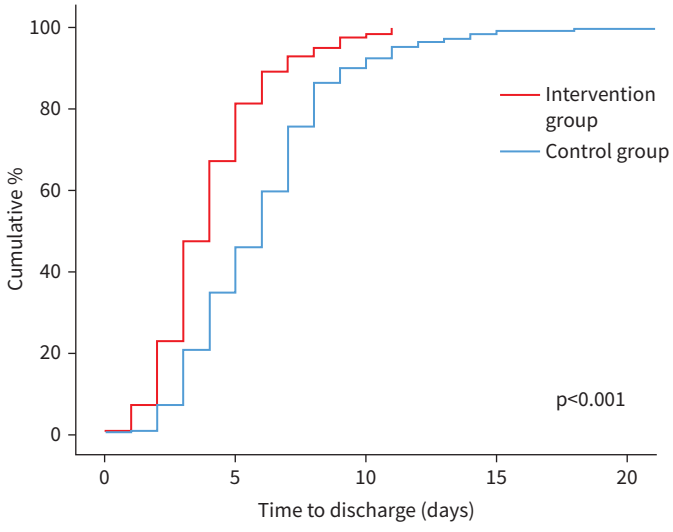

FIGURE 2 Cumulative frequency distribution curve for the time to discharge of patients in the intervention group as compared with those in the control group. Mann–Whitney U-test for comparison of medians.

TABLE 3 Prognostic tests among subgroups

Prognostic test[#]	Intervention group				Control group		
	Total	Low risk	Intermediate-low risk	Intermediate-high risk	Total	Negative sPESI[¶]	Positive sPESI[¶]
Subjects, n	249	60	159	30	249	83	166
Cardiac troponin	198	12 (20)	156 (98)	30 (100)	236	74 (89)	162 (98)
Brain natriuretic peptide	77	12 (20)	53 (33)	12 (40)	76	22 (27)	54 (32)
Heart-type fatty acid binding protein	0	0	0	0	0	0	0
Lactate	53	7 (12)	39 (25)	7 (23)	53	15 (18)	38 (23)
Echocardiography	116	6 (10)	80 (50)	30 (100)	112	34 (41)	78 (47)
Lower limb ultrasound testing	96	11 (18)	70 (44)	15 (50)	183	55 (66)	128 (77)

Data presented as n (% of risk-stratified or sPESI-classified group), unless otherwise stated. sPESI: simplified Pulmonary Embolism Severity Index. [#]: reimbursement for the performance of prognostic tests and for hospitalisation (based on estimations from the Spanish Ministry of Health, Consumer Affairs and Social Services): cardiac troponins (EUR 6), brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (EUR 12), heart-type fatty acid binding protein (EUR 10), lactate (EUR 2), transthoracic echocardiography (EUR 212), lower limb ultrasound testing (EUR 174), 1-day ward (EUR 526) and 1-day intensive care unit (EUR 1136); [¶]: *post hoc* calculation of the sPESI score by the study authors.

have implications for patients, for cost saving for patients and insurers and for reducing the burden on the healthcare system.

Society guidelines and scientific statements recommend assessing the severity of PE at initial presentation [10, 12, 13]. Prior studies have used clinical prognostic scores to assess the safety of outpatient management in patients with low-risk PE [10, 16, 17]. Further, a combination of biomarkers and imaging tests suggestive of RV dysfunction have been employed as inclusion criteria in clinical trials that evaluated the utility of thrombolytic therapy in normotensive patients with PE [18]. To our knowledge, this is the first randomised trial to test the impact of upfront objective risk assessment in an unselected group of patients with normotensive PE, followed by a recommended management pathway for early safe discharge.

The great variability seen in LOS for PE might reflect the variability in timeliness of ancillary testing, or the perceived benefits of prolonged in-hospital monitoring. Therefore, the first step of our pathway comprised formal risk stratification. Similar to previous studies, our results demonstrated the validity of the prognostic classification of PE severity [19, 20]. In the intervention arm, we observed increased mortality according to the determined risk groups, ranging from 0% in the low-risk group to 6.7% in the intermediate-high-risk group. Similar to previous studies showing the safety of early discharge for low-risk PE based on clinical criteria [21], this trial further supports the applicability of the sPESI for identifying low-risk patients with acute PE who might benefit from a brief hospital stay. Of note, at the time when the Intervención Pronóstica en la Embolia Pulmonar (IPEP) trial was being designed, home therapy of acute low-risk PE was not the standard of care, and the sPESI had not undergone sufficient validation. For this reason, the Steering Committee decided to use additional criteria for discharge (*i.e.* a cut-off value of heart rate $\geqslant$100 beats/min *versus* 110 beats/min).

The second step of our critical pathway included the use of objective and simple bedside criteria for mobilisation. Although early ambulation has been associated with shorter LOS and improved outcomes in other patient populations [22, 23], strategies of early mobilisation in patients with acute PE have not been evaluated in randomised trials. A previous study suggested an elevated risk for recurrent PE among those patients with intermediate-high-risk PE and residual venous thrombosis [24]. Such recurrent events could destabilise these marginally stable patients. Therefore, the trial protocol requested immediate mobilisation for low-risk patients and early mobilisation for intermediate-low-risk patients, but initial bed rest for intermediate-high-risk patients. Although we did not randomise patients in a factorial design to early ambulation, our results suggest the safety of early ambulation in most patients with acute PE. Finally, the third step of our intervention arm was based on the use of objective criteria to decide appropriateness for hospital discharge. In this regard, our study has shown that once stability is achieved in patients with acute PE, the risk of serious clinical deterioration is very low.

We explored whether the declining LOS over time is adversely associated with patient outcomes after hospital discharge. Using the data from hospital discharges with a diagnosis of PE from Pennsylvania

hospitals, Aujesky *et al*. [25] reported that patients with a short LOS had higher odds of post-discharge mortality. In the current randomised trial, however, compared with the control group we did not observe significant differences in the rates of hospital readmissions, all-cause and PE-related mortality or serious adverse events. While we cannot exclude the possibility of a small difference, the upper bound of 95% confidence intervals is not suggestive of clinically meaningful harm in this study. In addition, the rates of safety outcomes in IPEP are generally in line with those reported in previous trials. Future studies should also assess the impact of such interventions on long-term outcomes.

While the satisfaction with care was comparable between study groups, more than half of the patients in both arms did not express a high degree of satisfaction with care. This might be due to limitations with the single-question tool used in the study, limited health literacy or true deficiencies in the process of care. Future studies, using comprehensive, validated tools, should explore this finding.

In an era of cost containment and resource constraints in healthcare systems, cost-effective healthcare delivery is of paramount importance. The economic burden associated with PE remains substantial, and LOS is the most important driver of the cost in hospitalised patients [4]. In a study carried out in the USA, it has been estimated that eliminating 1 day during the course of a PE admission is potentially worth USD 1735 in economic benefits [26]. Therefore, our finding that the application of a prognostic assessment and management pathway reduced the LOS by 2 days compared with usual care may have significant economic implications. In addition, the use of a management strategy guided by early use of a prognostic pathway reduced the total cost of prognostic tests by 25% without compromising safety.

Our study has several limitations. First, it is possible that during the course of the study, the practice pattern of physicians treating patients in the control group may have been influenced by interactions with investigators treating those in the intervention arm. However, the influence of these interactions would probably have moved the differences in the LOS towards null. In fact, the mean LOS in the control group was substantially shorter than previously reported for PE patients treated in Spain [9]. Because the trial was conducted by collaborators enthusiastic about evidence-based management of PE, we might expect that the effect of early prognostication and subsequent management on the LOS would be even greater among clinicians with less experience. Second, we should clarify that our study did not include certain subgroups of patients with acute PE (*e.g.* high-risk (massive) PE, pregnant patients) and also excluded a quarter of patients with normotensive PE. Therefore, the findings cannot be extrapolated to those patients. However, the baseline characteristics were comparable between our study and previous studies [27]. Third, because we did not use a factorial design, we are unable to comment on the effectiveness of the individual components of the intervention. Fourth, though previous studies have assessed the presence of free-floating thrombi on an imaging test to drive decisions for patient care, the study protocol did not consider the absence of mobile cardiac thrombi as a predefined criterion for mobilisation. However, this strategy did not translate into an increased risk of fatal or non-fatal recurrent PE. Fifth, this trial was neither designed nor powered to test the impact of the intervention on the reduction of hospital-acquired adverse events. Sixth, though the trial was not designed to assess optimal follow-up of patients with PE, it included two visits (with a physical examination) within the first 30 days after randomisation. Therefore, any PE outpatient pathway might include facilities for dedicated outpatient follow-up [28]. Finally, though the trial rated patient satisfaction with the EQ-5D-5L instrument (EuroQol), the study was not designed as a medico-economic trial and neither the incremental cost-utility ratio (costs per quality-adjusted life year gained) nor the incremental cost-effectiveness ratio (cost per rate of serious adverse event avoided) were evaluated.

In conclusion, in a population of normotensive adults with acute symptomatic PE requiring hospitalisation, the use of a prognostic assessment and management pathway was effective in reducing LOS, the costs of prognostic tests and total hospitalisation costs. Though adverse events were not significantly different between the two groups, the trial was underpowered to exclude clinically meaningful differences.

Acknowledgements: We express our gratitude to S&H Medical Science Service for their quality control data and logistic and administrative support.

This study is registered at ClinicalTrials.gov with identifier: NCT02733198. Individual de-identified participant data (including data dictionaries) will not be shared. The study protocol (including the statistical analysis plan) will be available.

Conflict of interest: D. Jiménez has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, Pfizer, ROVI and Sanofi; served as a

speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, ROVI and Sanofi; and has received grants for clinical research from Daiichi Sankyo, Sanofi and ROVI. C. Rodríguez has nothing to disclose. F. León has nothing to disclose. L. Jara-Palomares has served as an advisor or consultant for Actelion Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Leo Pharma, Menarini, Pfizer, GSK and ROVI. R. López-Reyes has nothing to disclose. P. Ruiz-Artacho has nothing to disclose. T. Elías has nothing to disclose. R. Otero has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Leo Pharma, Janssen Pharmaceutical Companies, Merck Sharp & Dohme Corp, ROVI and Sanofi; and received grants for clinical research from Leo Pharma and Bayer Hispania SL. A. García-Ortega has nothing to disclose. A. Rivas-Guerrero has nothing to disclose. J. Abelaria has nothing to disclose. S. Jiménez has nothing to disclose. A. Muriel has nothing to disclose. R. Morillo has nothing to disclose. D. Barrios has nothing to disclose. R. Le Mao has nothing to disclose. R.D. Yusen has received research funding from Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Pfizer and Portola in the past 3 years; and has served as a consultant for Bayer HealthCare, Inc., Bristol-Myers Squibb, GlaxoSmithkline, Janssen, Johnson and Johnson, Ortho Pharmaceuticals, Organon, Pfizer, Portola, Sanofi and SCIOS in the past 3 years. B. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of inferior vena cava filters. M. Monreal has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Daiichi Sankyo, Leo Pharma and Sanofi; served as a speaker or a member of a speakers' bureau for Bayer HealthCare Pharmaceuticals, Daiichi Sankyo, Leo Pharma and Sanofi; and received grants for clinical research from Sanofi and Bayer. J.L. Lobo has nothing to disclose.

Support statement: Funded by the Instituto de Salud Carlos III and cofinanced by the European Development Regional Fund "A way to achieve Europe". Funding information for this article has been deposited with the Crossref Funder Registry.

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