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Randomized 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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Take-home message: The use of a prognostic assessment and management pathway reduces the length of hospital stay for PE.

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

Results: Of 500 patients who underwent randomization, 498 were included in the modified intention-to-treat analysis. The median LOS was 4.0 days (interquartile range [**IQR**], 3.7 to 4.2 days) in the intervention group and 6.1 days (IQR, 5.7 to 6.5 days) in the control group (P<0.001). The mean total cost of prognostic tests was €174.76 in the intervention group, as compared with €233.12 in the control group (mean difference, €-58.37; 95% confidence interval [**CI**], €-84.34 to €-32.40). The mean total hospitalization cost per patient was €2,085.66 in the intervention group, compared with €3,232.97 in the control group (mean difference, €-1,147.31; 95% CI, €-1,414.97 to €-879.65). No significant differences were observed in 30-day readmissions (4.0% vs. 4.8%, respectively), or all-cause (2.4% vs. 2.0%) and PE-related mortality rates (0.8% vs. 1.2%).

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

Trial Registration: ClinicalTrials.gov Identifier: NCT02733198.

Key Words: Pulmonary embolism, prognosis, LOS, mortality.

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 health care system in the United States more than $1.5 billion/year (3), with much of these enormous expenses being related to the period of hospital stay (4-7). A study that included patients hospitalized at Brigham and Women's Hospital from September 2003 to May 2010 estimated that the mean total hospitalization cost for a patient with PE was $8,764 (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), duration of hospitalization is still inexplicably high (9). Therefore, validation of strategies aimed at safely reducing the LOS are of paramount importance.

Since 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 those without hypotension, patients 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).

There are no randomized trials that 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 multicenter, randomized 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 hospitalized patients with acute PE.

METHODS

Trial design and oversight

From April 15, 2016, to December 15, 2019, we conducted a multicenter, randomized, open-label trial comparing a prognostic assessment and management pathway including risk stratification, followed by predefined criteria for mobilization and hospital discharge (intervention group) vs. usual care (control group) among outpatients hospitalized with acute PE. The institutional review board at each of the participating sites approved the protocol, which is available in the online 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 9 academic hospitals across Spain. Adults (age, ≥18 years) who required hospitalization for objectively diagnosed, acute symptomatic PE were eligible. Patients were excluded if they were pregnant; or if they had hemodynamic 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.

Randomization

Investigators randomized eligible patients by a centralized, Web-based system in a 1:1 ratio to either the intervention group or control group, in permuted blocks of 4 and 6, stratified according to trial site. Given the nature of the intervention, clinicians and research personnel were aware of trial-group assignments after randomization.

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) mobilization and (3) hospital discharge (Supplementary Appendix).

Patients in the intervention arm required to be risk stratified. Within 6 hours of randomization, trial investigators measured vital signs (i.e., heart rate, systolic blood pressure and oxygen saturation) to calculate the simplified Pulmonary Embolism Severity Index (s**PESI**) (15). An sPESI score of 0 identified low-risk patients. Patients with a sPESI $\geq$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 an sPESI $\geq$1 and abnormality for only troponin levels or only echocardiographic RV dysfunction (or neither) comprised the intermediate-low risk group. In turn, patients with an sPESI $\geq$1 and both elevated troponin levels and echocardiographic RV dysfunction comprised the intermediate-high risk group (**Table S1** in the Supplementary Appendix).

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

Predefined criteria for discharge were meeting criteria for mobilization, adequate vital signs (systolic blood pressure >100 mm Hg, heart rate <100/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 mobilization 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 hospitalization, and 30-day event rates for readmissions, as well as 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 radiologic confirmation of PE. We also assessed the patient satisfaction with the care received for acute PE. Surviving patients rated their satisfaction with their overall care for PE with visual scale 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 is 80 to 100. A list of the prespecified 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 P value of less than 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 with the use of the t-test, the Mann-Whitney U test, Fisher's exact test, or the chi-squared test, as appropriate. The trial was designed to enroll 250 patients in each group. Allowing for a loss to follow-up of 10 percent, this number provided the study with a power of 80 percent 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 a standard deviation of 7.5 days in LOS in both groups. The statistical analyses were performed with the use of the SPSS software package (version 26.0, SPSS) and Stata (version 16.1; StataCorp).

RESULTS

Patients

From April 15, 2016, to December 15, 2019, a total of 651 patients underwent screening, 500 patients underwent randomization 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 less than 50 percent of the patients were women. The characteristics of the patients at baseline did not differ significantly between the two trial groups (**Table 1**).

Intervention

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

The median time from randomization to the initiation of mobilization was 2.0 days (interquartile range, 1.5 to 2.0) in the intervention group and 2.0 days (interquartile range [**IQR**], 2.0 to 2.0) in the usual care group (P<0.01). In the intervention group, the median time from randomization to the initiation of mobilization 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 mobilization was not performed in 4 patients in the low-risk intervention group, who were thought to be too ill to be mobilized. Six patients in the intermediate-low risk group were mobilized in the first morning after randomization.

End points

Table 2 summarizes the outcomes for study patients. In the modified intention-to-treat analysis, the median LOS was 4.0 days in the intervention group vs. 6.1 days in the usual care group (P<0.001) (**Figure 2**). For patients randomized to the intervention group, the median LOS was 2.0 days (IQR, 1.0 to 3.0) in the low-risk category, 4.0 days (IQR, 3.0 to 5.0) in intermediate-low risk category, and 5.0 days (IQR, 4.0 to 6.0) in intermediate-high risk category (**Table S2** in the Supplementary Appendix). Assignment to the prognostic assessment and management pathway significantly reduced the use of prognostic tests: 88% in the intervention group (95% confidence interval [**CI**], 83.3 to 91.7%), as compared to 99% (95% CI, 95.4 to 99.3%) in the control group (**Table 3**). This difference translated into a significant difference in the mean total cost of prognostic tests: €174.76 in the intervention group, as compared with €233.12 in the control group (mean difference, €-58.37; 95% CI, €-84.34 to €-32.40). The mean total hospitalization cost per patient was €2,085.66 in the intervention group, compared with €3,232.97 in the control group (mean difference, €-1,147.31; 95% CI, €-1,414.97 to €-879.65).

Thirty-day follow-up data were available for all patients. As detailed in **Table 2**, all-cause readmission rates were similarly low in both groups. Thirty-day all-cause (2.4 vs. 2.0%; relative risk, 1.21; 95% CI, 0.36 to 4.00) or PE-related mortality (0.8 vs. 1.2%; relative risk, 0.66; 95% CI, 0.11 to 4.01) were not significantly different in the intervention and control groups. **Table S3** in the Supplementary Appendix summarizes 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 differences were found in satisfaction between groups: intervention

group, 45 of 147 (30.6%; 95% CI, 23.3 to 38.7%), vs. usual care group, 54 of 152 (35.5%; 95% CI, 27.9 to 43.7%).

Sensitivity analysis and subgroups

The results with respect to the intervention effect were consistent in analyses of the per-protocol cohort (**Table S4**). Further, findings were similar across the pre-defined subgroups (**Figure S1**).

DISCUSSION

This randomized, 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 mobilization and early hospital discharge to be safe, and associated with reduction in downstream laboratory or echocardiographic testing, and that it was effective in reducing LOS by 2 days, compared with usual care. These changes resulted in a net reduction in the mean hospitalization costs. Results were consistent across the study subgroups and in per-protocol analyses. These findings may have implications for patients, 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 randomized trial to test the impact of upfront objective risks 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 of 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 brief hospital stay. Of note, at the time when the 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 $\geq$100/min vs. 110/min).

The second step of our critical pathway included the use of objective and simple bedside criteria for mobilization. Although early ambulation has been associated with shorter LOS and improved outcomes in other patient populations (22, 23), strategies of early mobilization in patients with acute PE have not been evaluated in randomized 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 destabilize these marginally stable patients. Therefore, the trial protocol requested immediate mobilization for low-risk patients; early mobilization for intermediate-low risk patients; but initial bed rest for intermediate-high risk patients. Although we did not randomize 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 and colleagues reported that patients with a short LOS had higher odds of post-discharge mortality (25). In the current randomized 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, and serious adverse events. While we cannot exclude the possibility of a small difference, the upper bound of 95% confidence intervals is not suggestive of a 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 in both study groups, more than half of the patients in both arms did not express 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 health care systems, cost-effective health care delivery is of paramount importance. The economic burden associated with PE remains substantial, and LOS is the most important driver of the cost in hospitalized patients (4). In a study carried out in the United States, it has been estimated that eliminating a day during the course of a PE admission is potentially worth $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 toward null. In fact, the mean LOS in the control group was substantially shorter than previously reported for PE patients treated in Spain (9). Since 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, since a factorial design was not used, 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 mobilization. Anyway, 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 reduction of hospital-acquired adverse events. Sixth, though the trial was not designed to assess optimal follow-up of patients with PE, it included 2 visits (with a physical examination) within the first 30-days after randomization. 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, the study was not designed as a medico-economic trial and nor the incremental cost-utility ratio (costs per quality-adjusted life year gained) or 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 hospitalization, the use of a prognostic assessment and management pathway was effective in reducing LOS, the costs of prognostic tests, as well as total hospitalization costs. Though adverse events were not

significantly different in the two groups, the trial was underpowered to exclude clinically meaningful differences.

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Declaration of interests

D.J. 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; received grants for clinical research from Daiichi Sankyo, Sanofi and ROVI.

C.R. has nothing to disclose.

F.L. has nothing to disclose.

L.J-P. has served as an advisor or consultant for Actelion Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Leo Pharma, Menarini, Pfizer, and ROVI.

R.L-R. has nothing to disclose.

P.R-A. has nothing to disclose.

T.E. has nothing to disclose.

R.O. has served as an advisor or consultant for Bayer HealthCare Pharmaceuticals, Leo Pharma, Janssen Pharmaceutical Companies, Merck Sharp & Dohme Corp, ROVI and Sanofi; received grants for clinical research from Leo Pharma and Bayer Hispania SL.

A.G-O. has nothing to disclose.

A.R-G. has nothing to disclose.

J.A. has nothing to disclose.

S.J. has nothing to disclose.

A.M. has nothing to disclose.

R.M. has nothing to disclose.

D.B. has nothing to disclose.

R.L-M. has nothing to disclose.

R.Y. has received research funding from Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Pfizer, and Portola in the past 3 years. He has served as a consultant for Bayer HealthCare, Inc., Bristol-Myers Squibb, Glaxo-Smithkline, Janssen, Johnson & Johnson, Ortho Pharmaceuticals, Organon, Pfizer, Portola, Sanofi, and SCIOS in the past 3 years.

B.B. reports that he serves as a consulting expert (on behalf of the plaintiff) for litigation related to a specific type of inferior vena caval filters.

M.M. 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; received grants for clinical research from Sanofi and Bayer.
J. L. L. has nothing to disclose.

Table 1. Baseline Characteristics of the Patients.

Characteristic	Intervention Group (N=249)	Control Group (N=249)
Age – yr		
Mean	66.0	65.4
95% Confidence interval	64.0-68.1	63.3-67.5
Range	19-92	18-92
Sex – no. (%)		
Male	126 (51)	128 (51)
Female	123 (49)	121 (49)
Medical history – no. (%)		
Previous VTE	41 (16)	31(12)
Cancer †	48 (19)	50 (20)
Recent surgery ‡	31 (12)	34 (14)
Immobilization §	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 – no. (%)		
Dyspnea	199 (80)	207 (83)
Chest pain	123 (50)	121 (49)
Hemoptysis	17 (7)	17 (7)
Syncope	34 (14)	36 (15)
Systolic blood pressure – mm Hg		
Mean	136.9	137.2
95% Confidence interval	134.3-139.5	134.5-139.9
Heart rate – beats/min		
Mean	92.5	93.7
95% Confidence interval	90.1-94.9	91.2-96.1
Arterial oxyhemoglobin saturation - %		
Mean	91.9	92.8
95% Confidence interval	91.1-92.8	91.9-93.7
Simplified PESI* – no. (%)		
Low-risk	88 (35)**	83 (33)
High-risk	161 (65)	166 (67)
Risk stratum – no. (%)		
Low-risk	60 (24)	-
Intermediate-low risk	159 (64)	-

Intermediate-high risk	30 (12)	-
Hemoglobin – g/dl		
Mean	13.6	13.6
95% Confidence interval	13-4-13.9	13.4-13.9
Serum creatinine – mg/dl		
Mean	1.0	1.0
95% Confidence interval	0.9-1.0	0.9-1.0
Medications for the acute episode – no. (%)		
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)

Abbreviations: VTE, venous thromboembolism; PESI, Pulmonary Embolism Severity Index.

† Active or under treatment in the last year.

‡ In the previous month.

§ Immobilized patients defined as non-surgical patients who had been immobilized (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).

**28 patients had additional tests ordered in the emergency department that qualified them as intermediate-risk.

Table 2. End points.

Outcomes	Intervention Group (N=249)	Control Group (N=249)	Difference or Relative Risk (95% CI)†
Length of hospital stay - days			-2.1 (-2.6 to -1.7)
Median	4.0	6.1	
Interquartile range	3.7-4.2	5.7-6.5	
Cost of prognostic tests - €			-58.37 (-84.34 to -32.40)
Mean	174.76	233.12	
95% confidence interval	155.99-193.52	215.08-251.17	
Cost of hospitalization - €			-1,147.31 (-1,414.97 to -879.65)
Mean	2,085.66	3,232.97	
95% confidence interval	1,947.75-2,223.58	3,002.81-3,463.13	
30-day readmission rate - no. (%)	10 (4.0)	12 (4.8)	0.83 (0.35 to 1.95)
30-day all-cause mortality - no. (%)	6 (2.4)	5 (2.0)	1.21 (0.36 to 4.00)
30-day PE-related mortality - no. (%)	2 (0.8)	3 (1.2)	0.66 (0.11 to 4.01)
30-day serious adverse events - no. (%)	10 (4.0)	7 (2.8)	1.45 (0.54 to 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)	
Hemodynamic collapse	2 (0.8)	4 (1.6)	
Others*	2 (0.8)	0	

Abbreviations: CI, confidence interval; PE, pulmonary embolism.

†Difference (intervention – control) is shown for means. Relative risk (intervention:control) is shown for percentages.

*Purpura and pneumonia.

Table 3. Prognostic tests among subgroups.

Prognostic test	**Intervention group (N=249)**				**Control group (N=249)**		
	Total	*Low-risk* (N=60)	*Intermediate-low risk* (N=159)	*Intermediate-high risk* (N=30)	Total	Negative sPESI* (N=83)	Positive sPESI* (N=166)
Cardiac troponin - no. (%)	198	12 (20)	156 (98)	30 (100)	236	74 (89)	162 (98)
Brain natriuretic peptide - no. (%)	77	12 (20)	53 (33)	12 (40)	76	22 (27)	54 (32)
Heart-type fatty acid binding protein - no. (%)	0	0	0	0	0	0	0
Lactate - no. (%)	53	7 (12)	39 (25)	7 (23)	53	15 (18)	38 (23)
Echocardiography - no. (%)	116	6 (10)	80 (50)	30 (100)	112	34 (41)	78 (47)
Lower limb ultrasound testing - no. (%)	96	11 (18)	70 (44)	15 (50)	183	55 (66)	128 (77)

Abbreviations: sPESI, simplified Pulmonary Embolism Severity Index.

Reimbursement for the performance of prognostic tests and for hospitalization (based on estimations from the Spanish Ministry of Health, Consumer Affairs and Social Services): cardiac troponins (€6), brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (€12), heart-type fatty acid binding protein (€10), lactate (€2), transthoracic echocardiography (€212), lower limb ultrasound testing (€174), one-day ward (€526), and one-day intensive care unit (€1,136).

*Post-hoc calculation of the sPESI score by the study authors.

Figure 1. Flowchart of the Trial.

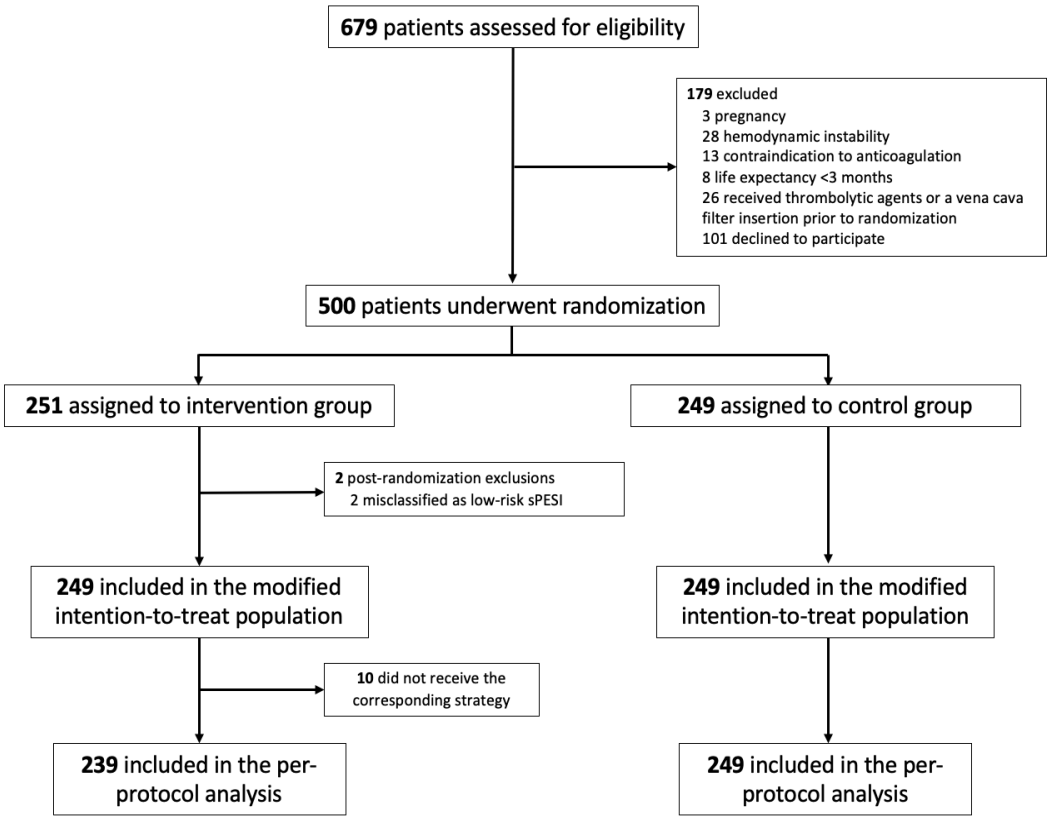
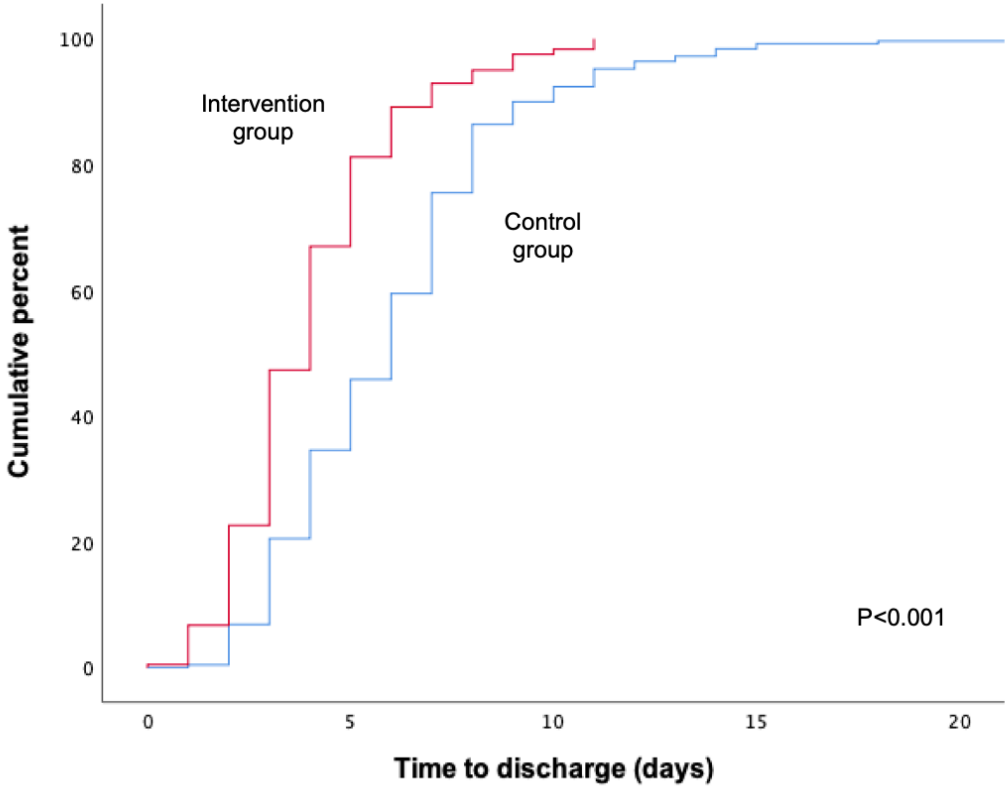


Figure 2. Cumulative Frequency Distribution Curve for the Time to Discharge of Patients in the Intervention Group as Compared with Those in the Control Group.



Mann-Whitney U test for comparison of medians.

Supplementary Appendix

Contents:

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Co-Chairmen (Principal Investigators): David Jiménez, Madrid (Spain), José Luis Lobo, Vitoria (Spain)

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Steering Committee: David Jiménez, Madrid (Spain), José Luis Lobo, Vitoria (Spain), Manuel Monreal, Badalona (Spain), Mikel Oribe, Galdakao (Spain), Remedios Otero, Sevilla (Spain), Fernando Uresandi, Bilbao (Spain), Roger Yusen, St. Louis (USA)

Data Safety Monitoring Board:
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Vicente Gómez del Olmo, Madrid (Spain)

Data Monitoring:
S&H Medical Science Service

Investigators: Barcelona (8 patients) – S. Jiménez (8 patients); Logroño (1 patient) – E. Hernando (1 patient); Lugo (1 patient) – L. Pérez-Llano (1 patient); Madrid (177 patients) – D. Jiménez/C.A. Quezada (139 patients), P. Ruiz-Artacho/J. Abelaira (37), J. de Miguel (1); Sevilla (156 patients) – L. Jara-Palomares/R. Otero/T. Elías (156 patients); Valencia (94 patients) – R. López-Reyes/A. García-Ortega (94 patients); Vitoria (63 patients) – J.L. Lobo/A. Rivas-Guerrero (63 patients).

Inclusion criteria

Patients were required to fulfill the following inclusion criteria:

- age 18 years or older;
- acute pulmonary embolism PE demonstrated by imaging as follows:
  - an intraluminal filling defect in segmental or more proximal branches on spiral computed tomography scan; or
  - a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan; or
  - an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram.

Exclusion criteria

Subjects who met any of the following criteria were excluded from randomization into the study:

- refusal to give informed consent;
- pregnancy;
- hemodynamic instability at presentation* (see below);
- contraindication to anticoagulant therapy;
- life expectancy <3 months;
- administration of thrombolytic agents, vena cava filter insertion or pulmonary thrombectomy within the previous 4 days;
- participation in any other investigational drug or device study in the past four weeks;
- geographic inaccessibility that precludes follow-up.

***Hemodynamic instability was defined as:**

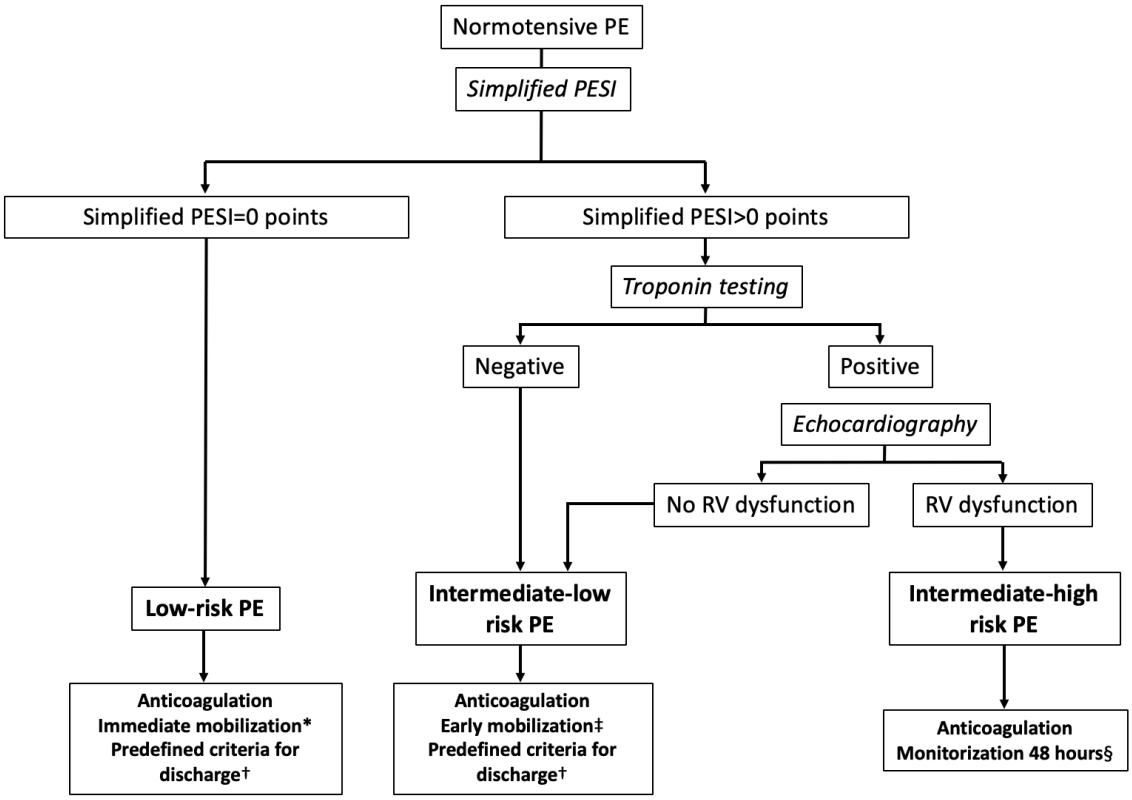
- need for cardiopulmonary resuscitation, or
- systolic blood pressure <90 mm Hg for at least 15 minutes; or
- need for catecholamine administration to maintain adequate organ perfusion and a systolic blood pressure of >90 mm Hg.

Prognostic assessment and management pathway

PE, pulmonary embolism

PESI, Pulmonary Embolism Severity Index

RV, right ventricle



Abbreviations: PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricle.

* Immediate mobilization was defined as ambulation for at least 20 minutes the first morning after randomization.

† Predefined criteria for discharge were meeting criteria for mobilization and adequate vital signs (systolic blood pressure >100 mm Hg, heart rate <100/min, and pulse oximetry >90%).

‡ Early mobilization was defined as ambulation for at least 20 minutes from the second morning after randomization, when they met the following objective criteria: systolic blood pressure >100 mm Hg, heart rate <100/min, and pulse oximetry >90%.

§ If there was no clinical deterioration within the first 48 hours, intermediate-high risk patients were managed the same way as intermediate-low risk patients.

Definition of study end points

Primary end point

Length of hospital stay: defined as the interval (in days) from diagnosis of PE at the emergency department to discharge (i.e., date of discharge minus date of diagnosis).

Secondary end points

Cost of prognostic tests and of hospitalization: we used the following reimbursement for the performance of prognostic tests and for hospitalization (based on estimations from the Spanish Ministry of Health, Consumer Affairs and Social Services): cardiac troponins (€6), brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (€12), heart-type fatty acid binding protein (€10), lactate (€2), transthoracic echocardiography (€212), lower limb ultrasound testing (€174), one-day ward (€526), and one-day intensive care unit (€1,136).

All-cause mortality

PE-related death: death was attributed to PE if there was no other explanation or there was autopsy or radiologic confirmation of PE.

Serious adverse event: an event that fulfils one or more of the following criteria:

- fatal;
- immediately life-threatening;
- results in persistent or significant disability/incapacity;
- requires or prolongs in-patient hospitalization;
- is a congenital anomaly/birth defect;
- any other reason representing a significant hazard comparable to the criteria mentioned above.

Recurrent PE: established by the presence of a new perfusion defect involving 75% or more of a lung segment on V/Q scintigraphy, or a new intraluminal filling defect or an extension of a previous filling defect on PE-protocol chest CT (1).

Major bleeding episodes: defined as those that required a transfusion of at least 2 units of blood, were retroperitoneal, intrapericardial, intraocular, spinal or intracranial, or were fatal (2).

Satisfaction with overall care for PE: surviving patients rated their satisfaction with their overall care for PE with visual scale 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 is 80 to 100. In addition, they rated their satisfaction with the EQ-5D-5L instrument (Spanish version).

Quality of life: surviving patients rated their quality of life with the Spanish version of PEmb-Qol (Spanish version).

Sample size estimation and interim analysis

Based on previous studies in pulmonary embolism and registry data, it was estimated that the median length of hospital stay in the control arm was 6.0 days. The trial was designed to enroll 250 patients in each group. Allowing for a loss to follow-up of 10 percent, this number provided the study with a power of 80 percent 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 percent level of significance, and a standard deviation of 7.5 days in both groups.

We conducted an interim analysis after recruitment of 50% of the study population. To preserve an overall type I error rate of 0.05 for the entire trial, the O'Brien-Fleming type boundary (alpha of 0.005) was used for early trial stoppage. Futility was assessed with conditional power, an approach that quantifies the probability of rejecting the null hypothesis of no effect. Stopping rule for futility was based on a conditional power less than 20% (3).

Simplified Pulmonary Embolism Severity Index

Variable	Points
Age >80 years	1
History of cancer	1
History of chronic cardiopulmonary disease	1
Pulse ≥110 beats/min	1
Systolic blood pressure <100 mm Hg	1
Arterial oxyhemoglobin saturation (SaO_2) <90%	1

A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥1, high risk.

Table S1. Criteria for positivity of prognostic tests.

Test	Criteria for positivity
Simplified PESI	A total point score ≥1 identifies high-risk sPESI patients
Cardiac troponin I or T, or high-sensitivity troponin T	Troponin I: Abbott, >0.05 ng/mL Troponin T: Roche, 30 pg/mL High-sensitivity troponin T: Roche, >14 pg/mL
Brain natriuretic peptide*	Abbott, >100 pg/mL Roche, >125 pg/mL
N-terminal pro-brain natriuretic peptide*	Roche, >125 pg/mL Roche, >300 pg/mL
Heart-type fatty acid binding protein	Hycult Biotech, >6 ng/mL
Lactate	Radiometer Medical A/S, ≥2 mmol/L Roche, ≥2.25 mmol/L
Computed tomography*	The study protocol defined CT-assessed RV enlargement as a ratio of the RV to the left LV short-axis diameters of greater than 0.9.
Echocardiography	The study defined echocardiographic RV dysfunction as the presence of a TAPSE ≤16 mm; or at least two of the following: dilation of the right ventricle (end-diastolic diameter >30 mm from the parasternal view or the right ventricle appearing larger than the left ventricle from the subcostal or apical view), hypokinesis of the right ventricle free wall (any view), or tricuspid regurgitant jet velocity >2.6 m/s.
Lower limb ultrasound testing	Vein incompressibility was the sole diagnostic criterion for DVT.

Abbreviations: sPESI, simplified Pulmonary Embolism Severity Index; CT, computed tomography; RV, right ventricle; LV, left ventricle; TAPSE, tricuspid annular plane systolic excursion; DVT, deep vein thrombosis.

*If these tests were available (and positive) before enrollment, investigators attending patients in the intervention arm were instructed to confirm the finding by means of transthoracic echocardiography.

Table S2. Clinical end points according to the risk stratum in the intervention arm.

Outcomes	Low-risk (N=60)	Intermediate-low risk (N=159)	Intermediate-high risk (N=30)
Length of hospital stay - days			
Median	2.0	4.0	5.0
Interquartile range	1.0-3.0	3.0-5.0	4.0-6.0
Cost of prognostic tests - €			
Mean	56.93	193.65	310.27
95% confidence interval	32.73-81.13	170.57-216.73	278.05-342.49
Cost of hospitalization - €			
Mean	1,122.13	2,312.94	2,808,13
95% confidence interval	995.88-1,248.38	2,144.36-2,481.53	2,454.02-3,162.25
30-day readmission rate - no. (%)	0	9 (5.7)	1 (3.3)
30-day all-cause mortality - no. (%)	0	4 (2.5)	2 (6.7)
30-day PE-related mortality - no. (%)	0	0	2 (6.7)
30-day serious adverse events - no. (%)	0	5 (3.1)	5 (17)

Abbreviations: PE, pulmonary embolism.

Table S3. Reasons for readmission and causes of death.

	Intervention group	Control group
Readmission	Cancer: 2 patients Bleeding: 2 patients Exacerbation of chronic obstructive pulmonary disease: 2 patients Fever: 2 patients Recurrent PE: 2 patients	Cancer: 3 patients Exacerbation of chronic obstructive pulmonary disease: 3 patients Bleeding: 2 patients Recurrent PE: 1 patient Exacerbation of congestive heart failure: 1 patient Fever: 1 patient Non-specific chest pain: 1 patient
Death	PE: 2 patients Cancer: 2 patients Bleeding: 1 patient Renal failure: 1 patient	PE: 3 patients Cancer: 1 patient Bleeding: 1 patient

Abbreviations: PE, pulmonary embolism.

Table S4. Clinical end points in the per-protocol population.

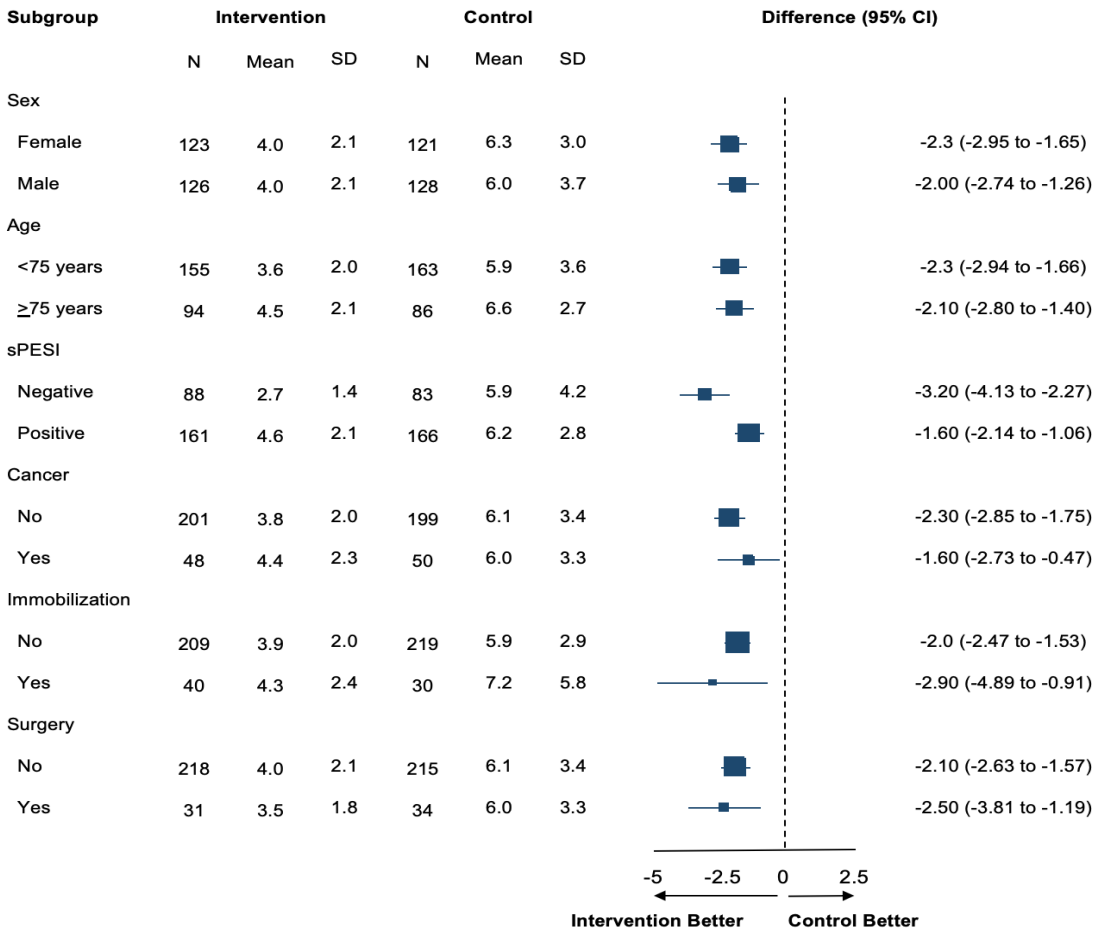
Outcomes	Intervention Group (N=239)	Control Group (N=249)	Difference or Relative Risk (95% CI)†
Length of hospital stay - days			-2.1 (-2.6 to -1.6)
Mean	4.0	6.1	
95% confidence interval	3.8-4.3	5.7-6.5	
Cost of prognostic tests - €			-55.03 (-81.31 to -28.75)
Mean	178.09	233.12	
95% confidence interval	158.86-197.33	215.08-251.17	
Cost of prognostic tests - €			-1,112.86 (-1,384.97 to -840.75)
Mean	2,120.11	3,232.97	
95% confidence interval	1,978.63-2,261.59	3,002.81-3,463.13	
30-day readmission rate - no. (%)	10 (4.2)	12 (4.8)	0.86 (0.37 to 2.04)
30-day all-cause mortality - no. (%)	6 (2.5)	5 (2.0)	1.26 (0.38 to 4.17)
30-day PE-related mortality - no. (%)	2 (0.8)	3 (1.2)	0.69 (0.12 to 4.18)
30-day serious adverse events - no. (%)	10 (4.2)	7 (2.8)	1.51 (0.57 to 4.03)
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)	
Hemodynamic collapse	2 (0.8)	4 (1.6)	
Others*	2 (0.8)	0	

Abbreviations: CI, confidence interval; PE, pulmonary embolism.

†Difference (intervention – control) is shown for means. Relative risk (intervention:control) is shown for percentages.

*Purpura and pneumonia.

Figure S1. End points in prespecified subgroups.



Abbreviations: sPESI, simplified Pulmonary Embolism Severity Index

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