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Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation
A Randomized Clinical Trial

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IMPORTANCE Active search for pulmonary embolism (PE) may improve outcomes in patients hospitalized for exacerbations of chronic obstructive pulmonary disease (COPD).

OBJECTIVE To compare usual care plus an active strategy for diagnosing PE with usual care alone in patients hospitalized for COPD exacerbation.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted across 18 hospitals in Spain. A total of 746 patients were randomized from September 2014 to July 2020 (final follow-up was November 2020).

INTERVENTIONS Usual care plus an active strategy for diagnosing PE (D-dimer testing and, if positive, computed tomography pulmonary angiogram) (n = 370) vs usual care (n = 367).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of nonfatal symptomatic venous thromboembolism (VTE), readmission for COPD, or death within 90 days after randomization. There were 4 secondary outcomes, including nonfatal new or recurrent VTE, readmission for COPD, and death from any cause within 90 days. Adverse events were also collected.

RESULTS Among the 746 patients who were randomized, 737 (98.8%) completed the trial (mean age, 70 years; 195 [26%] women). The primary outcome occurred in 110 patients (29.7%) in the intervention group and 107 patients (29.2%) in the control group (absolute risk difference, 0.5% [95% CI, −6.2% to 7.3%]; relative risk, 1.02 [95% CI, 0.82-1.28]; *P* = .86). Nonfatal new or recurrent VTE was not significantly different in the 2 groups (0.5% vs 2.5%; risk difference, −2.0% [95% CI, −4.3% to 0.1%]). By day 90, a total of 94 patients (25.4%) in the intervention group and 84 (22.9%) in the control group had been readmitted for exacerbation of COPD (risk difference, 2.5% [95% CI, −3.9% to 8.9%]). Death from any cause occurred in 23 patients (6.2%) in the intervention group and 29 (7.9%) in the control group (risk difference, −1.7% [95% CI, −5.7% to 2.3%]). Major bleeding occurred in 3 patients (0.8%) in the intervention group and 3 patients (0.8%) in the control group (risk difference, 0% [95% CI, −1.9% to 1.8%]; *P* = .99).

CONCLUSIONS AND RELEVANCE Among patients hospitalized for an exacerbation of COPD, the addition of an active strategy for the diagnosis of PE to usual care, compared with usual care alone, did not significantly improve a composite health outcome. The study may not have had adequate power to assess individual components of the composite outcome.

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Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 1323

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Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and is associated with a huge economic burden for the health care system.[1,2] Patients may have exacerbations of COPD, defined as acute worsening of respiratory symptoms that results in additional therapy,[3,4] drives disease progression, and is associated with mortality.[5] Common triggers of exacerbations include infections, air pollution, and noninfectious factors,[6] although other clinical conditions may mimic the symptoms of exacerbation of COPD.[7]

Pulmonary embolism (PE) is reported to be prevalent in patients with exacerbation of COPD.[8-11] Because the diagnosis of PE based on clinical suspicion is not sufficiently accurate and computed tomography pulmonary angiogram (CTPA) is readily available at emergency departments, its use has significantly increased over the past 5 years in the US.[12] CTPA is a time-consuming and burdensome investigation associated with radiation exposure, contrast reactions, and high cost. In addition, the need for an active detection strategy for PE needs to be balanced against the risk of exposing additional patients to anticoagulation,[13] because the diagnosis may not always have clinical significance (ie, subsegmental PE).[14] Although observational studies and meta-analyses have assessed the prevalence of PE among patients who have exacerbations of COPD, to our knowledge, no clinical trials have evaluated whether an active search for PE might improve clinical outcomes.

The objective of the Significance of Pulmonary Embolism in COPD Exacerbations (SLICE) trial was to compare health outcomes in patients with exacerbations of COPD who required hospital admission and were randomized to undergo an active search for PE with the use of D-dimer test and CTPA or to receive usual care.

Key Points

Question Does an active search for pulmonary embolism (PE) improve outcomes in patients hospitalized for exacerbations of chronic obstructive pulmonary disease (COPD)?

Findings This multicenter randomized clinical trial included 746 patients who required hospitalization for exacerbation of COPD and were randomized to receive usual care plus an active strategy for diagnosing PE or usual care alone. The primary outcome (a composite of nonfatal symptomatic venous thromboembolism, readmission for COPD, or death within 90 days after randomization) occurred in 29.7% of patients in the intervention group vs 29.2% in the control group, a difference that was not statistically significant.

Meaning Among patients hospitalized for an exacerbation of COPD, addition of an active diagnostic strategy for PE to usual care compared with usual care alone did not improve a composite set of health outcomes.

Methods

Trial Design and Oversight

This multicenter, open-label, randomized clinical trial was conducted from September 2014 through July 2020 in accordance with a previously published protocol,[15] which is provided in Supplement 1. The statistical analysis plan is provided in Supplement 2. The institutional review board at each of the participating sites approved the protocol, and each patient provided written informed consent.

Trial Sites and Patient Population

The trial was conducted in 18 academic hospitals across Spain. Patients were eligible for inclusion if they had a diagnosis of COPD and were hospitalized for an exacerbation. Patients were excluded if PE was the initial clinical suspicion (no suspicion of PE was defined as a patient in whom the physician-in-charge would not have examined for PE outside the study) or if they were pregnant; had a contraindication to CTPA; had a diagnosis of pneumonia, pneumothorax, or lower respiratory tract infection; or needed invasive mechanical ventilation at the time of hospital admission. Complete lists of inclusion and exclusion criteria are provided in eTables 1 and 2 in Supplement 3.

Randomization

Eligible patients were randomized in a 1:1 ratio to undergo usual care plus an active search for PE (intervention group) or usual care alone (control group). The permuted block (4 and 6 patients per block) randomization sequence was prepared by a statistician who was not involved in the trial. To minimize randomization bias, we performed randomization concealment with an interactive web-based response system until randomization was finished on the system through a computer. Given the nature of the intervention, clinicians and research personnel were aware of trial group assignments after randomization.

Trial Interventions

All patients received standard clinical management (usual care) for their exacerbation of COPD according to the inpatient clinician's preference and local standards (eFigure 1 in Supplement 3). Typically, standard clinical management consisted of the use of supplemental oxygen, short-acting inhaled β_2 agonists and short-acting anticholinergic agents, systemic corticosteroids, antibiotics, and pharmacological thromboprophylaxis.

Patients in the intervention group underwent D-dimer testing within 12 hours after randomization. Cutoff levels for defining elevated D-dimer were established by the department of clinical chemistry at each participating site (eTable 3 in Supplement 3). For patients with a negative D-dimer value, a diagnosis of PE was ruled out. For patients with a positive D-dimer value, a CTPA was performed (eTable 4 in Supplement 3). CTPA results were categorized as positive for PE if an intraluminal filling defect was seen in subsegmental or more proximal branches and considered negative if no filling defect was observed. Scans were considered technically inadequate only if main or lobar pulmonary vessels were not visualized. Although it was not mandatory, the protocol suggested the use of complete lower limb compression ultrasonography to detect concomitant deep vein thrombosis (DVT) for patients with isolated subsegmental PE.

If the diagnosis of PE was confirmed, patients received anticoagulant treatment according to guideline recommendations: parenteral anticoagulation (ie, unfractionated heparin, low-molecular-weight heparin, or fondaparinux) overlapped with and followed by vitamin K antagonists, parenteral anticoagulation followed by dabigatran or edoxaban, or monotherapy with apixaban or rivaroxaban for at least 3 months.

Outcome Measures

The primary outcome was assessed within 90 days after randomization and consisted of the composite of nonfatal new or recurrent symptomatic venous thromboembolism (VTE), readmission for COPD, or death. Secondary outcomes included death from any cause within 90 days after randomization, nonfatal new or recurrent symptomatic VTE within 90 days after randomization, readmission for exacerbation of COPD within 90 days after randomization, and length of hospital stay.

Confirmation of new or recurrent symptomatic PE required symptoms of PE and a new or an extension of a previous intraluminal-filling defect in subsegmental or more proximal branches on CTPA. Confirmation of new or recurrent symptomatic DVT required symptoms of DVT and the following criteria: in the absence of previous DVT investigations at baseline, a noncompressible venous segment on ultrasonography; if there were previous DVT investigations at baseline, abnormal lower limb compression ultrasonography where compression had been normal; or, if previously noncompressible, a substantial increase (>4 mm) in diameter of the thrombus during full compression.

Evaluation of adverse events within 90 days after randomization included major bleeding, clinically relevant nonmajor bleeding, and serious adverse events. Major bleeding was defined according to the guidelines of the International Society of Thrombosis and Hemostasis as acute clinically overt bleeding associated with 1 or more among the following: a decrease in hemoglobin of 2 g/dL or more, a transfusion of 2 or more units of packed red blood cells, bleeding that occurs in at least 1 of the critical sites (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), bleeding that is fatal (defined as a bleeding event that the central independent committee adjudicate as the primary cause of death or contributing directly to death), and bleeding that necessitates surgical intervention.[16] A bleeding event was classified as a clinically relevant nonmajor bleeding event if it was overt (ie, symptomatic or visualized by examination), did not meet the criteria for major bleeding, required medical attention, or was associated with discomfort for the patient, such as pain or impairment of activities of daily life. Serious adverse events were those that fulfilled 1 or more of the following criteria: fatal, immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged in-patient hospitalization, was a congenital anomaly/birth defect, or any other reason representing a significant hazard comparable to the criteria mentioned above.

A central independent adjudication committee whose members were unaware of treatment randomization adjudicated all suspected events during the study period. Trial visits were scheduled at enrollment and at 7, 30, and 90 days after randomization.

Sample Size Calculation

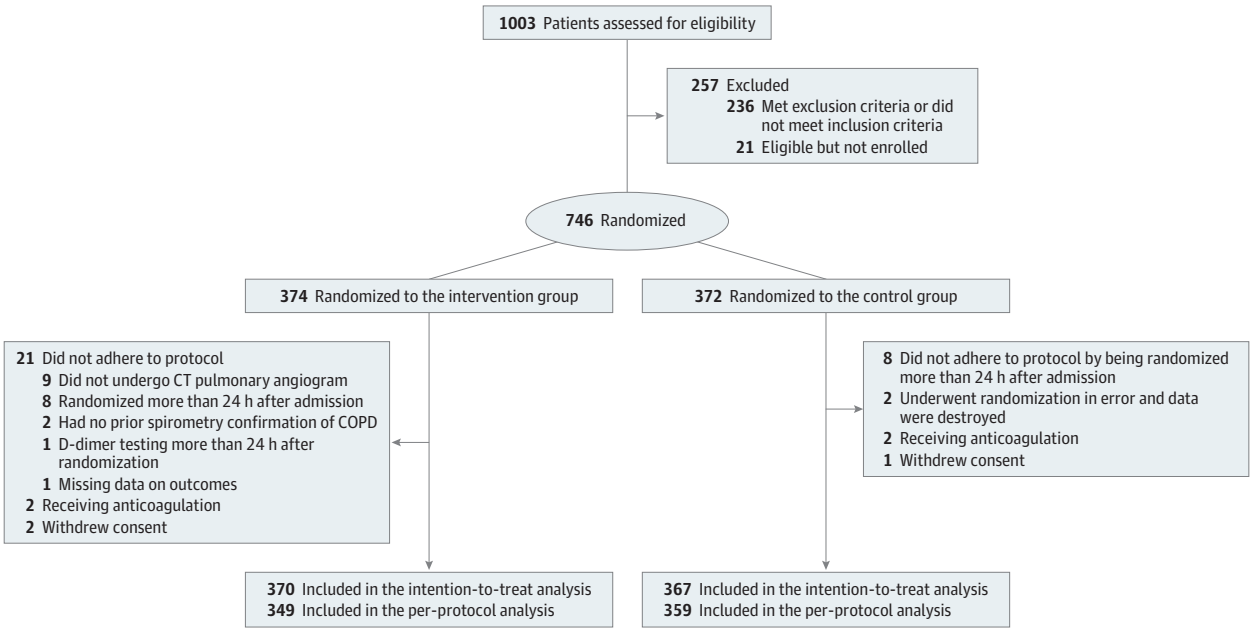
For a prevalence of PE of 10%, the event rate for the primary outcome was calculated to be 40%.[17,18] An estimated 355 participants were needed in each trial group to detect a 10% absolute reduction in the primary outcome (ie, from 40% to 30%) with 80% power at a 2-sided 5% significance level. The 10% reduction was based on consultation with general practitioners and pulmonologists, who considered this reduction to be clinically important. We initially aimed to enroll 900 patients to compensate for a 25% dropout rate. An interim analysis was conducted after recruitment of 50% of the study population. To preserve an overall type I error rate of .05 for the entire trial, the O'Brien-Fleming-type boundary (α of .005) was used for early trial stoppage.

Statistical Analysis

The characteristics of the patients at baseline are reported as percentages for categorical variables and as mean (SD) and median (IQR) values for continuous variables, as appropriate. All patients who underwent randomization were included in the efficacy and safety analyses according to the treatment group to which they were assigned. In addition, safety analyses were performed among the safety analysis set, which included all patients in the control group and all patients in the intervention group who underwent D-dimer testing. Missing data were not replaced, and analyses included all evaluable patients. Because only 1 patient was lost to follow-up (in the intervention group), sensitivity analyses were performed on the primary and secondary outcomes using worst-case scenario (ie, all participants lost to follow-up had the outcome). The analyses of the primary and secondary outcomes were also replicated in the per-protocol population. In addition, subgroup analyses were carried out according to age, sex, COPD severity, hospital size, and season (Supplement 2).

The primary efficacy and safety outcome data were analyzed by means of a 2-sided χ^2 test of proportions. A post hoc analysis was applied to account for a possible clustering effect at the enrolling site level. For this purpose, a mixed-effect model including site of enrollment as a random effect was performed. In another post hoc analysis, we examined whether an age-adjusted D-dimer cutoff, defined as age (in years) multiplied by 10 in patients 50 years or older, was associated with an increased diagnostic yield of D-dimer in this population. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Kaplan-Meier survival curves until 90 days after randomization were compared with a log-rank test. The significance threshold was 2-sided at .05. All statistical analyses were performed with the use of the SPSS/PC software package, version 26 (SPSS), and Stata software, version 16.1 (StataCorp).

Figure 1. Flow of Patients in a Study of the Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes



Results

After 450 patients underwent randomization, a predefined interim analysis showed a 3% dropout rate that was lower than anticipated, and the data and safety monitoring board recommended to decrease the sample size to 746 (to account for a 5% dropout rate) and to continue the trial to the end.

Patients

From September 2014 through July 2020, a total of 1003 patients were screened for inclusion in the trial, of whom 746 (74.4%) underwent randomization (**Figure 1**). Four patients were receiving anticoagulants at the time of randomization, 3 patients withdrew consent to use their data, and 2 underwent randomization in error, which left 370 patients in the intervention group and 367 in the usual care group. Overall, the mean (SD) age was 70.4 (9.9) years, and 195 (26%) patients were women. The demographic and clinical characteristics of the patients at baseline did not differ between the 2 trial groups (**Table 1**). All patients in the control group and all patients in the intervention group without PE during the initial diagnostic period received at least 1 prophylactic dose of low-molecular-weight heparin.

Trial Interventions

Overall, 369 of 370 patients (99.7%) randomized to the intervention group received a D-dimer test within 12 hours after randomization, and the median (IQR) D-dimer value was 560 (353-1055) ng/mL. Among these 369 patients, 183 (49.6%) had negative D-dimer values and a diagnosis of PE was ruled out. A CTPA was performed in 11 patients (6.0%) with a negative D-dimer value and a segmental PE was diagnosed in 1 patient (0.5% [95% CI, 0.0%-3.0%]). Although none of these patients had a clinical suspicion of PE at the time of randomization, investigators sped up the trial procedures and ordered a CTPA before being aware of the results of the D-dimer test. Among the 186 patients with a positive D-dimer value, a CTPA was performed in 181 (97.3%). CTPA findings showed PE in 16 patients (8.8% [95% CI, 5.1%-14.0%]): central in 7 patients (43.8%), segmental in 7 patients (43.8%), and multiple subsegmental in 2 patients (12.4%). No patients underwent a compression ultrasonography. Therefore, the prevalence of PE among the 192 patients who underwent a CTPA was 8.9% and the overall rate of PE found in the intervention group during the initial diagnostic period was 17 of 370 patients (4.6% [95% CI, 2.7%-7.3%]). Eleven (65% [95% CI, 38%-86%]) of these patients received low-molecular-weight heparin overlapped with and followed by vitamin K antagonists, 4 (24% [95% CI, 6.8%-50%]) received apixaban, and 2 (12% [95% CI, 1.5%-36%]) received rivaroxaban. None of these patients required fibrinolytic therapy, surgical or percutaneous thrombectomy, or an inferior vena cava filter. CTPA findings that supported an alternative diagnosis were detected in 133 patients (76.0%) (eTable 5 in Supplement 3).

As per protocol, none of the 367 patients in the control group received workups for diagnosis of PE unless a suspicion of this diagnosis arose after randomization. Five patients in the control group underwent a CTPA because of suspicion for PE during the index admission, and PE was confirmed in 3 patients (all nonfatal).

Primary Outcome

At 90 days, 110 patients (29.7%) in the intervention group and 107 (29.2%) in the usual care group experienced the primary composite outcome (absolute risk difference, 0.5% [95% CI,

Table 1. Baseline Characteristics of Patients in a Study of the Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation

Characteristic	No. (%) Intervention group (n = 370)	Control group (n = 367)
Age, mean (SD), y	70.2 (9.9)	70.6 (9.9)
Sex		
Men	284 (76.8)	258 (69.7)
Women	86 (23.2)	109 (30.3)
Current smoker	119 (32.2)	111 (30.2)
Pack-years of smoking, mean (SD)	58.8 (27.1) [n = 119]	57.8 (26.6) [n = 111]
COPD exacerbations in the past 12 mo, mean (SD)	1.3 (1.8)	1.4 (1.6)
FEV_1 after administration of albuterol, mean (SD), % of the predicted normal value	46.2 (18.1)	45.8 (16.3)
COPD		
Very severe: <30% of the predicted normal value	56 (15.1)	58 (15.8)
Severe: 30% to <50% of the predicted normal value	170 (45.9)	162 (44.1)
Moderate: 50% to <80% of the predicted normal value	113 (30.5)	119 (32.4)
Mild: ≥80% of the predicted normal value	29 (7.8)	28 (7.6)
Previous treatment		
Long-acting β-agonist	329 (88.9)	337 (91.8)
Long-acting anticholinergic	313 (84.6)	319 (86.9)
Inhaled corticosteroid	267 (72.2)	277 (75.5)
Risk factors for VTE		
Immobilization[a]	67 (18.1)	66 (18.0)
Sleep apnea	56 (15.1)	55 (15.0)
Congestive heart failure	48 (13.0)	50 (13.6)
Cancer[b]	12 (3.2)	14 (3.8)
History of VTE	10 (2.7)	15 (4.1)
Surgery[c]	1 (0.3)	2 (0.5)
Clinical symptoms and signs at presentation		
Dyspnea	368 (99.5)	367 (100)
Heart rate >100/min	129 (34.9)	135 (36.8)
Increased sputum volume	129 (34.9)	127 (34.6)
Purulent sputum	24 (6.5)	24 (6.5)
Systolic blood pressure <100 mm Hg	12 (3.2)	8 (2.2)
Wells score		
Low clinical probability	163 (44)	162 (44)
Intermediate clinical probability	206 (56)	204 (56)
High clinical probability	1 (0.3)	1 (0.3)
pH	(n = 315)	(n = 326)
<7.35	45 (14)	63 (19)
7.35-7.45	222 (70)	226 (69)
>7.45	49 (16)	37 (11)
Pao_2, mm Hg		
≥60	161 (51)	148 (45)
50-59	92 (29)	106 (33)
<50	62 (20)	72 (22)
$Paco_2$, mm Hg		
≤45	167 (53)	161 (49)
46-55	81 (26)	74 (23)
>55	67 (21)	91 (28)
Spo_2 <90%	145 (40) [n = 367]	134 (37) [n = 365]
Admission blood tests		
Creatinine, mean (SD), mg/dL	0.9 (0.3)	0.9 (0.3)
Creatinine >1.5 mg/dL	6 (1.6)	12 (3.3)
Hemoglobin, mean (SD), g/dL	14.3 (2.1)	14.1 (1.8)
Leukocytes, mean (SD), $\times 10^9$/L	10.9 (7.1)	10.9 (4.6)
Treatment for exacerbation		
Short-acting inhaled β_2-agonists	364 (98)	366 (100)
Short-acting inhaled anticholinergics	370 (100)	365 (99)
Systemic corticosteroids	301 (81)	305 (83)
Antibiotics	249 (67)	270 (74)
Pharmacological thromboprophylaxis (LMWH)	370 (100)	367 (100)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

[a] In the previous month.

[b] Active or receiving treatment in the past year.

[c] Defined as nonsurgical patients who had been immobilized (ie, total bed rest with bathroom privileges) for ≥4 days in the month prior to exacerbation of COPD.

−6.2%-7.3%]; relative risk, 1.02 [95% CI, 0.82 to 1.28]; P = .86) (**Table 2**). The hazard ratio for the composite outcome within 90 days after randomization in the intervention group, compared with the usual care group, was 1.0 ([95% CI, 0.8-1.3]; P = .82) (**Figure 2**).

Secondary Outcomes

During the follow-up period, 15 patients (4.1%) in the intervention group and 18 patients (4.9%) in the control group underwent a CTPA because of suspicion for PE. Nonfatal new or recurrent symptomatic venous thromboembolism occurred in 2 patients (0.5%) in the intervention group and in 9 patients (2.5%) in the control group (risk difference, −2.0% [95% CI, −4.3%-0.1%]; relative risk, 0.22 [95% CI, 0.05-1.01]) (Table 2; eFigure 2 and eFigure 3 in Supplement 3). All thrombotic events were PEs (2 lobar in the intervention group and 1 central, 4 lobar, and 4 segmental in the control group). There was no evidence of a significant between-group difference in readmissions for an exacerbation of COPD: 94 of 370 patients (25.4%)

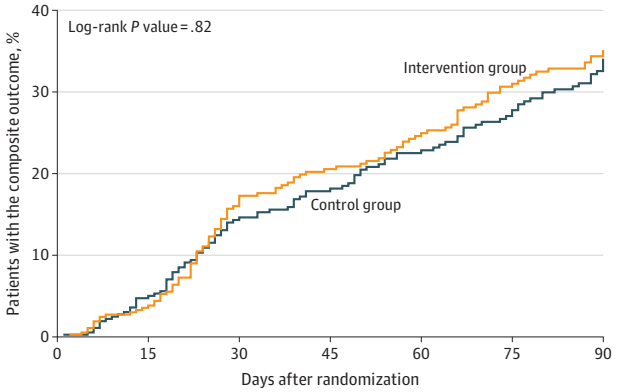
Table 2. Outcomes in a Study of the Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation

Outcome	No. (%)		Absolute difference (95% CI), %	Relative risk (95% CI)	*P* value
	Intervention (n = 370)	Control (n = 367)			
Primary outcome					
Composite of nonfatal new or recurrent symptomatic VTE, readmission for exacerbation of COPD, or death from any cause	110 (29.7)	107 (29.2)	0.5 (−6.2 to 7.3)	1.02 (0.82 to 1.28)	.86
Secondary outcomes					
Nonfatal new or recurrent symptomatic VTE	2 (0.5)	9 (2.5)	−2.0 (−4.3 to 0.1)	0.22 (0.05 to 1.01)	
Nonfatal new or recurrent DVT	0	0			
Nonfatal new or recurrent PE	2	9			
Readmission for exacerbation of COPD	94 (25.4)	84 (22.9)	2.5 (−3.9 to 8.9)	1.11 (0.86 to 1.43)	
Death from any cause	23 (6.2)	29 (7.9)	−1.7 (−5.7 to 2.3)	0.79 (0.46 to 1.43)	
Time to discharge, median (IQR), d	6.0 (4.0-9.0)	6.0 (4.0-8.0)		0.68 (−0.29 to 1.66)[a]	
Adverse events					
Major bleeding	3 (0.8)	3 (0.8)	0 (−1.9 to 1.8)	0.99 (0.20 to 4.88)	.99
Clinically relevant nonmajor bleeding	1 (0.3)	1 (0.3)	0 (−1.5 to 1.5)	0.99 (0.06 to 15.80)	
Serious adverse events	18 (4.9)	18 (4.9)	0 (−3.5 to 3.4)	0.99 (0.53 to 1.88)	

Abbreviations: COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Difference (intervention minus control) is shown for mean values.

Figure 2. Composite Outcome in a Study of the Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes



No. of patients at risk							
Control group	366	349	317	306	292	279	264
Intervention group	370	357	315	301	289	272	262

The median (IQR) observation time was 90 (70-90) days for the intervention group and 90 (76-90) days for the control group.

in the intervention group and 84 of 367 patients (22.9%) in the usual care group (risk difference, 2.5% [95% CI, −3.9%-8.9%]; relative risk, 1.11 [95% CI, 0.86-1.43]) (Table 2; eFigure 2 and eFigure 3 in Supplement 3). At 90 days, 23 patients (6.2%) in the intervention group and 29 (7.9%) in the control group died (risk difference, −1.7% [95% CI, −5.7%-2.3%]; relative risk, 0.79 [95% CI, 0.46-1.33]) (Table 2; eFigure 2 and eFigure 3 in Supplement 3). COPD was the most common cause of death in the 2 groups (eTable 6 in Supplement 3). The median (IQR) duration of hospitalization among patients was 6 (4-9) days in the intervention group and 6 (4-8) days in the control group.

Secondary and Subgroup Analyses

The results, with respect to the intervention effect, were consistent in safety and sensitivity analyses and in analyses of the per-protocol cohort (eTable 7 in Supplement 3). Further, findings were similar across the prespecified subgroups (eFigure 4 in Supplement 3). The estimate of the intervention effect for the primary outcome did not change when a post hoc mixed-effect model, including site of enrollment as random effect, was performed (odds ratio, 1.02 [95% CI, 0.74-1.40]). In a post hoc sensitivity analysis that used an age-adjusted D-dimer cutoff, 51 of 181 patients were reclassified into the

group with negative D-dimer values. Therefore, the use of the age-adjusted cutoff resulted in a 13.8% absolute increase in the percentage of negative D-dimer test results. One of the patients with a negative age-adjusted D-dimer result had a segmental PE.

Adverse Events

Major bleeding occurred in 3 of 370 patients (0.8%) in the intervention group and in 3 of 367 (0.8%) in the usual care group (risk difference, 0.0% [95% CI, −1.9% to 1.8%]; relative risk, 1.0 [95% CI, 0.2-4.9]; P = .99). There were no fatal bleeding episodes in the intervention group and 1 in the usual care group. The sites of major bleeding in the groups are reported in eTable 8 in Supplement 3. Clinically relevant nonmajor bleeding occurred in 1 patient (0.3%) in the intervention group and in 1 patient (0.3%) in the usual care group (risk difference, 0% [95% CI, −1.5% to 1.5%]; relative risk, 1.0 [95% CI, 0.1 to 15.8]). The percentages of patients experiencing serious adverse events were not significantly different in the two groups: 4.9% in the intervention group and 4.9% in the usual care group (risk difference, 0% [95% CI, −3.5% to 3.4%]; relative risk, 1.0 [95% CI, 0.5 to 1.9]).

Discussion

This multicenter randomized trial involving patients who required hospitalization for exacerbations of COPD showed that an active strategy for the diagnosis of PE (D-dimer testing and, if positive, CTPA) did not result in a lower percentage of patients having the composite outcome of nonfatal new or recurrent VTE, readmission for COPD, or death within 90 days after randomization. The lack of effect was observed using the complete data set with a low dropout rate, and it was supported by sensitivity and subgroup analyses.

The frequency of PE in the intervention group in this trial was similar to that in a previous study in which 3.3% of patients admitted to the emergency departments of 2 academic teaching hospitals for acute exacerbation of moderate to very severe COPD had concurrent PE[10] and lower than in a previous study in which the prevalence of PE detected via CT in 197 patients with COPD who were admitted to the hospital for severe exacerbation of unknown origin was 22%.[9] Study design, setting, and patient selection might account for the difference in PE prevalence between the study by Tillie-Leblond et al[9] and the current trial. The former was a single-center prospective study that was conducted in a large referral inpatient respiratory department. Therefore, it might not be representative of the patients treated by emergency physicians in general hospitals. Moreover, patients with COPD and an initial suspicion of PE were not excluded from the study, which potentially led to the selective enrollment of patients with a higher probability of PE and a high cancer rate of 29%. In addition, a 2021 cross-sectional study showed a very similar 4.3% prevalence of PE among patients who required hospitalization for exacerbation of COPD in whom PE was not suspected.[19]

Because one of the exclusion criteria in this trial was an initial clinical suspicion of PE, enrolled patients did not have high clinical probability of PE and pretest clinical probability assessment was deemed unnecessary in the diagnostic pathway. Accordingly, and because of its very high negative predictive value among patients with a low or intermediate clinical pretest probability,[20] the study chose to include D-dimer testing as the initial step. In the intervention group, half of the patients had PE ruled out by a D-dimer level lower than the predetermined cutoff value, with a low likelihood of subsequent symptomatic PE. Therefore, considering PE to be ruled out in patients with exacerbations of COPD who have a negative D-dimer test result seems appropriate. Although previous studies have shown that a D-dimer cutoff adjusted to patients' age might increase the clinical usefulness without compromising safety,[21,22] the trial used a fixed D-dimer cutoff. A post hoc sensitivity analysis showed that the use of an age-adjusted D-dimer cutoff resulted in a 14% absolute increase in the percentage of negative D-dimer test results in the intervention group with a very low 90-day VTE risk.

Episodes of new or recurrent VTE and death (which were components of the primary outcome) were numerically lower in the intervention group, and the results could not rule out an absolute decrease of 4.3% in new or recurrent VTE and 5.7% in new or recurrent mortality. All recurrences that were diagnosed in the follow-up period were PEs. This result is not unexpected, because patients with COPD and acute symptomatic VTE present more frequently with PE than with DVT, and those with a history of PE are at increased risk for recurrent PE (vs DVT).[23,24]

Although the trial showed that an active strategy for the diagnosis of PE was not beneficial, some clinicians use CTPA to detect potential alternative diagnoses. Similar to previous studies, CTPA identified an alternative diagnosis in a large proportion of patients in the study.[25] However, the alternative diagnosis had therapeutic consequences in only 23% of the patients, and specific treatments did not result in improvement in patient outcomes.

The strength of the study is that it was set in routine practice in a large, representative, mixed sample of hospitals to enhance generalizability. It was large enough study to provide estimates with reasonable precision in the overall study population. Although the patients and clinicians could not be blinded, the trial used central, blind adjudication of outcomes. Very few patients were lost to follow-up, allowing the intention-to-treat principle to be met.

Limitations

This study has several limitations. First, the observed frequency of PE in the intervention group was lower than expected, and the results do not rule out the possibility of a clinically important treatment effect. However, the trial was designed on the premise that a sizable protective effect would be needed to justify the costs and risks of a CTPA. In addition, the trial was not powered to show a possible favorable difference in new or recurrent VTE or all-cause mortality, which would have required a very large sample size. Second, because the study had an open-label design, there is potential for diagnostic suspicion bias, in which clinicians more often suspect a new (or recurrent) VTE event if the patient has not

undergone a CTPA.[26] Nonetheless, the absolute number of patients with suspected recurrence was low and not significantly different in the 2 groups. Third, the findings in the study population might not apply to other patients with COPD. However, the inclusion and exclusion criteria were intended to be consistent with the pattern of patients admitted to the hospital with exacerbations of COPD. Fourth, the inclusion of readmission for COPD in the composite outcome might be questioned because it is less clinically important than VTE or death. Because some of these readmissions might be secondary to PE, and ordering a CTPA for every readmitted patient was deemed infeasible, it was felt to be justified to including these events in the composite to ascertain the effect of the intervention on diagnosed and potentially undiagnosed PE events.

Conclusions

Among patients hospitalized for an exacerbation of COPD, the addition of an active strategy for the diagnosis of PE to usual care, compared with usual care alone, did not significantly improve a composite health outcome. The study may not have had adequate power to assess individual components of the composite outcome.

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