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Original Research

Long-Term Outcomes of Patients With Pulmonary Embolism Managed With Endovascular Therapies Compared to Medical Therapy

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ABSTRACT

Background: Guidelines on the management of acute pulmonary embolism (PE) recommend consideration of endovascular therapies (EVT) for patients at intermediate-high risk. However, long-term data on the outcomes of patients after EVT as compared to medical therapy is lacking. This study aimed to compare outcomes of patients receiving EVT as compared to medical therapy alone at 3 to 6 months.

Methods: In this single-center, retrospective cohort study, 190 patients with PE underwent evaluation for presence of right ventricular (RV) dysfunction by transthoracic echocardiogram, residual perfusion defects on ventilation-perfusion scanning, and functional capacity by 6-minute walk distance (6MWD) at 3 to 6 month follow-up.

Results: Fifty-eight (31%) patients received EVT for the management of their acute PE. At follow-up (median 120 [97-170] days), 71% of patients who received EVT had normalization of RV function compared with only 34% of patients who received medical therapy alone ($P < .001$). Patients who received EVT had a significantly greater increase in their estimated glomerular filtration rate ($P = .001$), decrease in N-terminal proB-type natriuretic peptide ($P = .003$), and decrease in hemoglobin values ($P = .018$). Patients with intermediate-high to high risk PE who received EVT had significantly greater distance achieved on their 6MWD as compared to those who received medical therapy alone ($P = .025$).

Conclusions: Patients with acute PE who received EVT plus medical therapy were more likely to achieve normalization of RV dysfunction at 3 to 6 month follow-up compared to patients who received medical therapy alone. These data suggest that EVT is an effective therapy option for acute PE in intermediate-high and high risk patients with potential durable long-term benefits.

Introduction

Acute pulmonary embolism (PE) has a heterogenous clinical presentation. Patients at low risk of decompensation present with hemodynamic stability, preserved right ventricular (RV) size and function, and no evidence of myocardial necrosis. Conversely, hemodynamic instability at presentation is associated with in-hospital mortality rates exceeding 15%.[1,2] In high risk PE patients, systemic thrombolysis improves hemodynamic parameters, pulmonary artery pressures, RV function, and short-term cardiovascular outcomes.[3,4] However, the use of systemic thrombolysis is associated with significant increases in major bleeding complications.[3,4] In patients presenting with intermediate-risk PE (hemodynamically stable with RV dysfunction with or without elevated cardiac biomarkers) or patients who are at increased risk of major bleeding, the best course of action remains unclear.

After initial stabilization of acute hemodynamic changes, the goal of PE treatment is directed toward improvement in symptoms, oxygenation, and RV function. Data suggests that endovascular therapies (EVT) may more rapidly restore vital sign abnormalities and oxygen requirement than medical therapy alone.[5] Additionally, the development of

Abbreviations: 6MWD, 6-minute walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; CT, computed tomography; EVT, endovascular therapy; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal proB-type natriuretic peptide; PE, pulmonary embolism; PESI, pulmonary embolism severity index; TTE, transthoracic echocardiogram; V/Q, ventilation-perfusion.

Keywords: clinical outcomes; endovascular therapy; pulmonary embolism; pulmonary hypertension.

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chronic thromboembolic pulmonary hypertension (CTEPH) following treatment of acute PE is of great clinical concern. Two prospective studies totaling 460 patients found the rates of CTEPH to be between 3.8% and 4.8% at 2 years after initial diagnosis.[6,7] The diagnosis of CTEPH is often difficult to make and as a result is frequently delayed.[8] Recovery of RV function, both in-hospital and in follow-up, has served as an important marker of not only short-term mortality but also as a potential predictor of CTEPH in patients that remain symptomatic after PE.[9–12]

Over the past decade, there has been increased interest in the use of EVT; however, data on long-term outcomes remain limited. In small randomized controlled trials (RCTs) and prospective cohort studies, the use of EVT compared with heparin-based treatments resulted in improvements in RV function without increasing bleeding risk.[13–15] A meta-analysis found that EVT had a lower rate of major bleeding and similar mortality rates as systemic thrombolysis.[16] However, the follow-up duration for these trials were short (ie, within 24 or 48 hours), and the long-term effects of EVT compared to anticoagulation alone are poorly understood. In this analysis, we sought to compare the effects of EVT plus medical therapy vs medical therapy alone at 3 to 6 month follow-up in patients who presented with acute PE.

Methods

Patient selection

From January 2017 through December 2020, all consults to the University of Chicago PE Response Team (PERT) were retrospectively analyzed. Of the 643 consults, 236 (37.2%) patients had an outpatient follow-up ≥90 days from the consult date. Only outpatient visits to a dedicated PE follow-up clinic or with a pulmonologist, cardiologist, or specialized pulmonary hypertension expert were included. All applicable patients were scheduled for follow-up in our multidisciplinary PE follow-up clinic. Patients with low risk PE, PERT consult for an issue other than acute PE, out-of-network insurance status, and presentation to the hospital for trauma-related issues were excluded from an automatic follow-up appointment. Patients without an initial contrast-enhanced computed tomography (CT) scan, with a poor functional status (defined as being bed bound or living in a nursing home), who had <1 year prognosis as determined by the reviewing physician, or who did not complete follow-up imaging (CT or transthoracic echocardiogram [TTE]) were excluded from analysis (Figure 1).

Baseline data

Baseline demographic characteristics including age, sex, and self-identified race were collected at the time of the initial consult. Respiratory rate, heart rate (HR), oxygen saturation (O_2 sat), temperature, and systolic (SBP) and diastolic blood pressure (DBP) were measured at the time of first presentation to the emergency department. Hypotension was defined as SBP <90 mm Hg or >40 mm Hg lower than the last outpatient recording for longer than 15 minutes. Baseline medical history and laboratory data (estimated glomerular filtration rate [eGFR], N-terminal proB-type natriuretic peptide [NT-proBNP], troponin, and hemoglobin) were obtained from chart review at the time of the initial consult. After August 2018, a high-sensitivity troponin assay replaced the traditional troponin assay at our institution. Because traditional troponin values are measured in ng/mL while high-sensitivity troponin values are measured in ng/L, traditional troponin values were multiplied by 1000 to compare to high-sensitivity troponin. Troponin values below the limit of detection were set to a value of 6 ng/L (the limit of detection). eGFR was calculated based on the 2021 race-free equation from the chronic kidney disease epidemiology collaboration (CKD-EPI).[17] The presence of RV dysfunction was defined as either increased RV size (defined as RV/left ventricular ratio [LV] > 1.0) on contrast-enhanced CT read by a board-certified radiologist or decreased RV function or increased RV size on TTE read by a board-certified cardiologist. Patients were categorized into 4 risk groups based on the European Society of Cardiology (ESC) 2019 guidelines on the diagnosis and management of acute PE.[18] Patients with high risk were defined as those who presented with cardiac arrest, systolic BP <90 mm Hg or systolic BP drop of ≥40 mm Hg for >15 minutes. Intermediate-high risk patients were

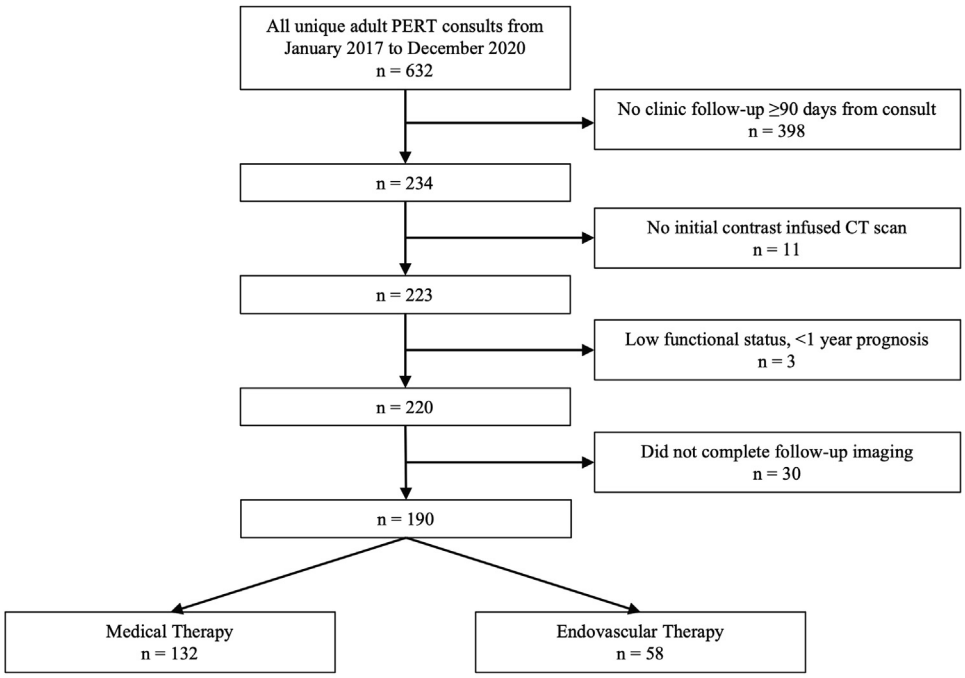


Figure 1.
Exclusion cascade.

defined as those with presence of RV dysfunction and elevated cardiac troponin values. Intermediate-low risk patients were defined as those with either elevated cardiac troponin values or the presence of RV dysfunction but not both. Low risk patients were all others. The pulmonary embolism severity index (PESI) and simplified PESI (sPESI) score was calculated for each patient using previously validated methods.[19–21] Patients were defined as having received EVT if they underwent mechanical thrombectomy or catheter-directed thrombolysis. The decision to treat with EVT is made after risk stratification and a discussion with all stakeholders involved including the patient, interventional cardiology, pulmonary/critical care medicine, radiology, and emergency medicine. The modality and device chosen was at the discretion of the interventionalist.

Follow-up

At outpatient clinic follow-up, vital signs (HR, respiratory rate, SBP, DBP, and O_2 sat), laboratory data, imaging and diagnostic testing (TTE, contrast-enhanced CT, ventilation-perfusion [V/Q] scan, and 6-minute walk test [6MWD]), and the presence and nature of symptoms were recorded. Change in laboratory data was defined as the value at clinic follow-up subtracted by the value at the time of the initial consult. Symptoms were defined as either pleuritic chest pain, shortness of breath, or dyspnea on exertion. The presence of RV dysfunction was defined in the same way as at initial presentation. RV dysfunction improvement was defined as the presence of RV dysfunction at the time of the initial consult and no presence of RV dysfunction at follow-up testing. The distance achieved on 6MWD was defined as the amount of distance walked during the total 6-minute test or the amount of distance achieved prior to stopping due to symptoms.

Statistical analysis, sensitivity analysis, and subgroup analysis

All analyses and visualizations were performed with "tidyverse," "tableone," and "sjPlot" packages in R 4.1.2 (R Core Team, 2021). Differences between medical therapy and EVT were compared using χ^2 test for categorical variables and *t* test for continuous variables with normal distributions. Continuous variables with nonnormal distributions were compared using the Mann-Whitney *U* test. All 2-tailed *P* values < 0.05 were considered statistically significant. Prespecified subgroup analysis by ESC risk group (high/intermediate-high and low/intermediate-low), PESI score, sex, and self-identified race (Black versus non-Black) was also performed. A sensitivity analysis was performed with exclusion of high risk patients as defined by the ESC risk groups. Intermediate-high risk PESI scores were defined as class III, IV, or V (corresponding to a score $\geq$86) while low risk PESI scores were defined as class I or II (corresponding to a score $<$86).[19] An sPESI $\geq$1 was defined as high risk, while an sPESI score of 0 was defined as low risk.[21]

Results

Baseline

Of 632 PERT consults during the 4-year inclusion period, 190 (30.1%) were included for final analysis (Figure 1). Of the included patients, 58 (30.5%) underwent EVT. The mean age was 57 ± 18 years, 120 (63%) were female, 150 (79%) self-identified as Black, and the median body mass index (BMI) was 31 [26-37]. Table 1 presents baseline demographic characteristics stratified by type of therapy received. There were no significant differences in age, sex, race, BMI, or medical history between the patients. Patients who underwent EVT were significantly more likely have faster HR (108 vs 100 beats per minute, $P = .009$), lower O2 sats (94% vs 96%, $P = .028$), presence of RV dysfunction (97% vs 67%, $P < .001$), and higher hemoglobin (13.2 vs 11.6 g/dL, $P < .001$) compared with those receiving medical therapy alone. Patients receiving EVT were also significantly more likely to be classified as intermediate-high or high risk by the ESC risk stratification model compared to medical therapy patients (57% vs 37%, $P = .002$). Only 1 patient who received EVT was classified as ESC low risk. There was significant overlap in PESI scores between patients receiving EVT vs medical therapy alone (Figure 2). Four patients, all in the medical therapy group, were not discharged on any anticoagulation at the discretion of the treating physician.

Follow-up

The median time to first outpatient clinic follow-up was 120 [97-170] days. At follow-up, 71% (n = 41) of patients who received EVT had normalization of their RV compared to 28% (n = 45) of patients who were treated with medical therapy alone ($P < .001$). As shown in Table 2, there was no significant differences in absolute eGFR or NT-proBNP values between the EVT and medical therapies groups. Patients receiving EVT had significantly greater improvement in eGFR (+9.6 vs -0.9 mL/min/1.73 m^2, $P = .001$), decrease in hemoglobin (-0.4 vs +0.5 g/dL, $P = .018$), and decrease in NT-proBNP (-1192 vs -150 pg/mL, $P = .003$) compared to those receiving medical therapy alone. There were no significant differences in the presence of symptoms, presence of any perfusion defects on V/Q scans, or 6MWD between the EVT and medical therapy groups.

Sensitivity and subgroup analysis

Subgroup analysis comparing EVT plus medical therapy to medical therapy alone by ESC risk categories is presented in Table 3. Compared to medical therapy alone, EVT was associated with significantly higher normalization of RV dysfunction (76% vs 47%, $P = .018$), distance achieved on 6-minute walk (342 vs 272 meters, $P = .025$), and improvement in NT-proBNP (-2383 vs -594 pg/mL, $P = .027$) in intermediate-high or high risk patients. Among patients who were intermediate-low or low risk, EVT was associated with significant improvement in eGFR (+10.4 vs -2.4 mL/min/1.73 m^2, $P = .001$), decrease in hemoglobin (-0.3 vs +0.6 g/dL, $P = .048$), and significantly higher normalization of RV function (64% vs 27%, $P = .001$). No significant difference was observed in 6MWD in the intermediate-low or low risk patients. Results were similar when stratified by PESI score, sex, and race (Supplemental Tables S1-S3). Patients who received catheter-directed thrombolytics had significantly lower presence of any perfusion defects on V/Q scan at follow-up compared to those who received mechanical thrombectomy (42.3% vs 91.7%, $P = .012$, Supplemental Table S4). Sensitivity analysis with the exclusion of high risk patients showed similar findings to the main analysis (Supplemental Table S5).

Discussion

In this retrospective study of long-term follow-up in patients presenting with acute PE, those treated with EVT plus medical therapy had significantly greater improvement in RV dysfunction compared to patients treated with medical therapy alone at 3 to 6 month follow-up (Central Illustration). At the time of PE diagnosis, patients receiving EVT had higher hemoglobin levels, higher NT-proBNP, and lower eGFR values, but at follow-up, there was no difference in these laboratory values between EVT and medical therapy groups. Patients who had received EVT experienced significantly greater improvements in NT-proBNP and eGFR and a small but statistically significant decrease in hemoglobin at clinic follow-up.

Table 1. Baseline data stratified by patients receiving medical therapy alone versus endovascular therapy.

	Medical therapy (n = 132)	Endovascular therapy (n = 58)	*P*
Age, y	58.2 ± 17.9	54.0 ± 16.8	.131
Female sex	83 (62.9)	37 (63.8)	>.99
Black race	108 (81.8)	42 (72.4)	.204
Body mass index, kg/m^2	30.1 [25.7, 35.3]	33.3 [26.8, 39.8]	.078
Medical history			
Smoking			
Never	68 (51.5)	34 (58.6)	.722
Former	29 (22.0)	12 (20.7)	
Current	35 (26.5)	12 (20.7)	
History of cancer	30 (22.7)	9 (15.5)	.348
Pulmonary disease	32 (24.2)	8 (13.8)	.152
Asthma	20 (15.2)	5 (8.6)	.321
Chronic obstructive pulmonary disease	14 (10.6)	4 (6.9)	.593
Pulmonary embolism	17 (12.9)	11 (19.0)	.386
Deep vein thrombosis	24 (18.2)	14 (24.1)	.454
Hypertension	76 (58.0)	29 (50.0)	.388
Coronary artery disease	14 (10.6)	5 (8.6)	.875
Peripheral artery disease	1 (0.8)	2 (3.4)	.46
Stroke	11 (8.3)	5 (8.6)	>.99
Diabetes	26 (19.8)	13 (22.4)	.836
Taking aspirin	39 (29.5)	12 (20.7)	.275
Taking P2Y12 inhibitor	3 (2.3)	2 (3.4)	>.99
Taking anticoagulation	10 (7.6)	7 (12.1)	.469
Taking β-blocker	28 (21.2)	9 (15.5)	.475
History of IVC filter	8 (6.1)	9 (15.5)	.068
Initial encounter			
Respiratory rate, breaths/min	20.0 [18.0, 23.0]	20.0 [18.2, 22.0]	.22
Heart rate, beats/min	100.0 [85.8, 114.2]	107.5 [94.0, 121.0]	.009
Temperature, °C	36.8 ± 0.6	36.7 ± 0.5	.161
Peripheral oxygen saturation, %	96.0 [93.0, 99.0]	94.0 [91.0, 98.0]	.028
Systolic blood pressure, mm Hg	129.9 ± 22.8	131.1 ± 20.7	.717
Diastolic blood pressure, mm Hg	77.9 ± 15.3	86.7 ± 15.8	<.001
Altered mental status	7 (5.3)	4 (6.9)	.924
Presence of hypotension	8 (6.1)	4 (6.9)	>.99
Presence of right ventricular dysfunction	88 (66.7)	56 (96.6)	<.001
ESC risk group			
High risk	8 (6.1)	4 (6.9)	.002
Intermediate-high risk	41 (31.1)	29 (50.0)	
Intermediate-low risk	52 (39.4)	24 (41.4)	
Low risk	31 (23.5)	1 (1.7)	
PESI score	86.2 ± 33.4	86.4 ± 28.1	.967
PESI class			
High risk	13 (10.3)	5 (9.1)	.464
Intermediate risk	45 (35.7)	25 (45.5)	
Low risk	68 (54.0)	25 (45.5)	
Simplified PESI score	1.2 ± 0.9	1.1 ± 1.0	.713
Simplified PESI class			
High risk	103 (78.0)	42 (72.4)	.519
Low risk	29 (22.8)	16 (28.6)	
Initial eGFR, mL/min/1.73 m^2	79.9 ± 28.6	73.0 ± 25.2	.118
Initial hemoglobin, g/dL	11.6 [9.7, 13.3]	13.2 [11.7, 14.0]	<.001
Initial NT-proBNP, pg/mL	602.5 [130.8, 1975.8]	943.0 [326.0, 2833.0]	.128
Initial troponin, ng/L	8.0 [0.1, 36.0]	18.5 [0.0, 44.0]	.531
Discharged on home oxygen	28 (21.2)	8 (13.8)	.317
Discharge anticoagulation			
Warfarin	24 (18.2)	13 (22.4)	.500
Apixaban	46 (34.8)	20 (34.5)	
Rivaroxaban	42 (31.8)	21 (36.2)	
Other	16 (12.1)	4 (6.9)	
None	4 (3.0)	0 (0.0)	

Values are mean ± SD, n (%), or median [IQR].
eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; IVC, inferior vena cava; NT-proBNP, N-terminal proB-type natriuretic peptide; PESI, pulmonary embolism severity index.

Previous studies have demonstrated that EVT is associated with improvement in RV dilation and function in the short-term (ie, 24-48 hours). A prospective cohort study of 150 patients with proximal PE and RV/LV ratio ≥0.9 treated with catheter-directed, low-dose fibrinolysis showed significant improvement in RV/LV ratio at 48 hours along with a decrease in mean systolic pulmonary artery pressure.[14] A subsequent cohort trial of 101 patients with intermediate-risk PE treated with EVT found significant improvement in RV/LV ratio at 48 hours.[15] A small RCT performed by Kucher et al[13] randomized 59 patients with acute main or lower lobar PE and RV/LV ratio ≥1.0 to receiving unfractionated heparin plus EVT with recombinant tissue plasminogen activator or unfractionated heparin alone. They found that patients treated with EVT had a significantly greater decrease in RV/LV ratio at 24 hours compared to patients treated with heparin alone. Importantly,

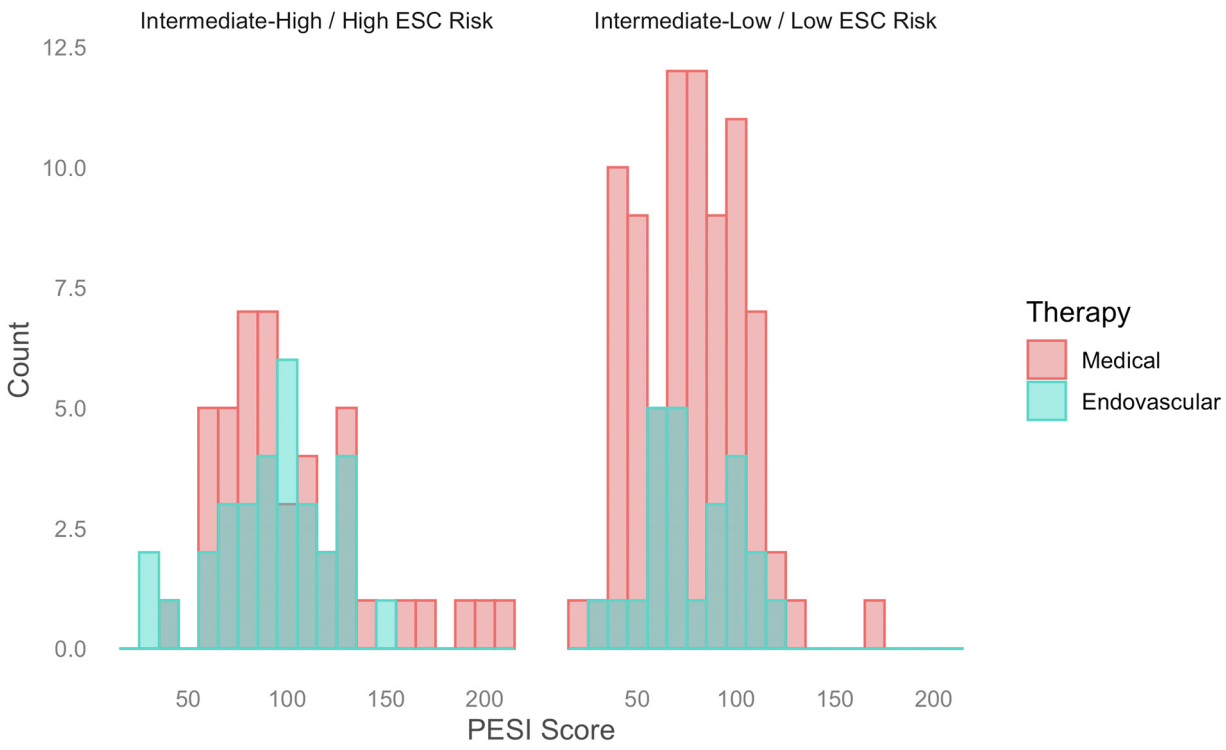


Figure 2.
Histogram of PESI scores in patients receiving medical therapy alone (red) vs endovascular therapy (green) stratified by ESC risk stratification. ESC, European Society of Cardiology; PESI, pulmonary embolism severity index.

they observed no difference in safety events including major and minor bleeding at 90 days between the treatment groups. Large, high quality RCTs comparing EVT plus anticoagulation versus anticoagulation alone are currently underway. As a result, multisocietal guidelines on the use of EVT remain mixed and controversial. The 2019 ESC guidelines on the management of acute PE upgraded its recommendation for EVT to Class IIb(C) in all high risk patients and in intermediate or low risk patients who deteriorate hemodynamically.[18] The 2021 CHEST guidelines for the management of venous thromboembolism give a weak recommendation for EVT in patients with hypotension with either high

Table 2. Clinic follow-up data stratified by patients receiving medical therapy alone vs endovascular therapy.

	Medical therapy (n = 132)	Endovascular therapy (n = 58)	*P*
Median days to clinic follow-up	117.5 [97.8, 160.0]	128.5 [95.0, 195.8]	.29
Presence of RV dysfunction	49 (37.1)	15 (25.9)	.178
Normalization of RV function	45 (34.1)	41 (70.7)	<.001
Completed V/Q Scan	75 (57.5)	40 (69.0)	.174
Presence of any perfusion defects on V/Q	34 (45.3)	22 (57.9)	.288
Completed 6-minute walk test	69 (52.3)	34 (58.6)	.515
6-minute walk test distance, meters	328.1 ± 107.3	349.6 ± 100.6	.332
Symptoms at follow-up	39 (30.0)	15 (25.9)	.686
Need for home oxygen	12 (9.2)	3 (5.2)	.52
Respiratory rate, breaths/min	16.2 ± 2.2	16.0 ± 2.1	.663
Heart rate, beats/min	80.0 [67.5, 90.0]	79.0 [64.0, 88.0]	.459
Peripheral oxygen saturation, %	98.0 [97.0, 100.0]	98.0 [97.0, 100.0]	.923
Systolic blood pressure, mm Hg	127.0 [111.0, 137.0]	130.0 [120.5, 138.0]	.136
Diastolic blood pressure, mm Hg	72.0 [61.2, 79.8]	78.0 [68.0, 85.5]	.007
Clinic anticoagulation			
Warfarin	21 (15.9)	11 (19.0)	.508
Apixaban	46 (34.8)	21 (36.2)	
Rivaroxaban	43 (32.6)	23 (39.7)	
Other	13 (9.8)	1 (1.7)	
None	9 (6.8)	2 (3.4)	
Follow-up eGFR, mL/min/1.73 m^2	79.5 ± 25.8	85.0 ± 25.5	.199
Follow-up hemoglobin, g/dL	12.0 ± 2.2	12.7 ± 1.8	.027
Follow-up NT-proBNP, pg/mL	121.0 [44.0, 470.0]	57.0 [28.0, 188.5]	.077
Change in eGFR, mL/min/1.73 m^2	-0.9 ± 18.4	9.6 ± 18.3	.001
Change in hemoglobin, g/dL	0.5 ± 2.4	-0.4 ± 1.8	.018
Change in NT-proBNP, pg/mL	-150.0 [-1047.5, -4.5]	-1192.0 [-3153.0, -344.5]	.003

Values are mean ± SD, n (%), or median [IQR].
eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal proB-type natriuretic peptide; RV, right ventricular; V/Q, ventilation-perfusion.

Table 3. Select baseline and follow-up characteristics stratified by European Society of Cardiology Risk Stratification.

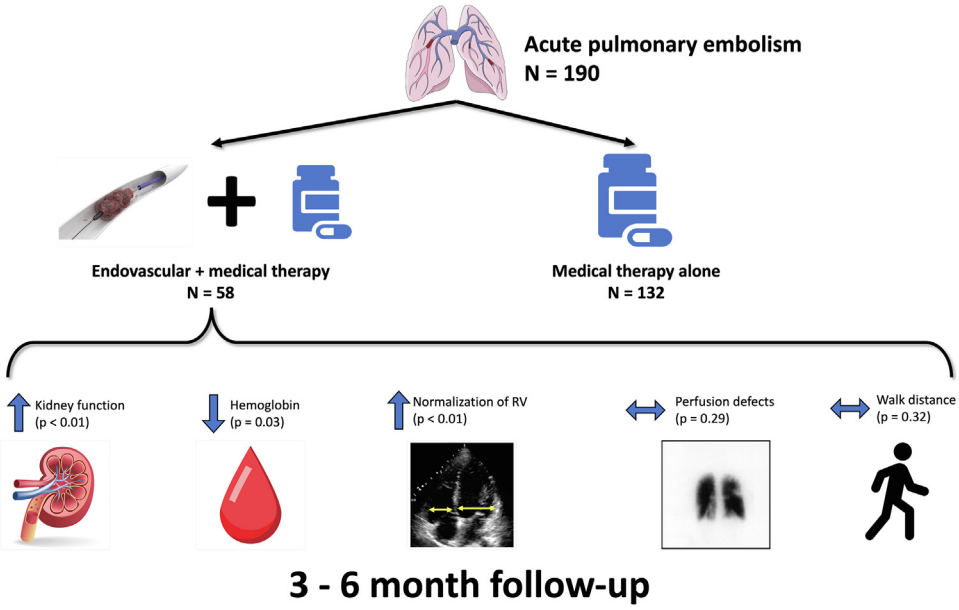
	Medical therapy	Endovascular therapy	*P* value
Intermediate-High or High Risk			
No. of patients	49	33	
Age, y	64.6 ± 19.0	56.2 ± 17.1	.048
Female sex	28 (57.1)	24 (72.7)	.229
Black race	44 (89.8)	25 (75.8)	.162
Body mass index, kg/m^2	30.7 [26.3, 35.1]	35.8 [27.0, 44.4]	.152
PESI score	102.6 ± 38.0	93.7 ± 29.9	.28
sPESI	1.5 ± 1.0	1.2 ± 1.1	.216
Initial eGFR, mL/min/1.73 m^2	68.8 ± 27.8	68.5 ± 27.1	.95
Follow-up eGFR, mL/min/1.73 m^2	73.3 ± 27.4	79.8 ± 28.3	.342
Change in eGFR, mL/min/1.73 m^2	1.8 ± 23.3	8.9 ± 18.2	.176
Initial NT-proBNP, pg/mL	1557.5 [518.0, 2885.5]	813.0 [334.2, 5096.5]	.908
Follow-up NT-proBNP, pg/mL	304.5 [128.8, 612.8]	63.0 [49.0, 232.5]	.027
Change in NT-proBNP, pg/mL	-594.0 [-1621.0, -67.5]	-2383.0 [-5675.0, -492.0]	.025
Initial hemoglobin, g/dL	11.7 ± 2.3	12.4 ± 1.6	.132
Follow-up hemoglobin, g/dL	11.8 ± 2.4	12.1 ± 1.7	.514
Change in hemoglobin, g/dL	0.3 ± 2.8	-0.4 ± 1.9	.263
Symptoms at follow-up	14 (28.6)	8 (24.2)	.857
Presence of RV dysfunction initial	48 (98.0)	33 (100.0)	>.99
Presence of RV dysfunction follow-up	25 (51.0)	8 (24.2)	.028
Normalization of RV function	23 (46.9)	25 (75.8)	.018
Presence of any perfusion defects on V/Q	19 (63.3)	16 (64.0)	>.99
6-minute walk test distance, meters	272.0 ± 101.5	341.9 ± 88.9	.025
Median days to clinic follow-up	109.0 [98.0, 128.0]	116.0 [93.0, 178.0]	.831
Intermediate-Low or Low Risk			
No. of patients	83	25	
Age, y	54.5 ± 16.1	51.2 ± 16.3	.373
Female sex	55 (66.3)	13 (52.0)	.29
Black race	64 (77.1)	17 (68.0)	.51
Body mass index, kg/m^2	29.8 [25.7, 35.3]	31.9 [27.3, 37.1]	.407
PESI score	77.1 ± 26.8	77.1 ± 22.9	.991
sPESI	1.0 ± 0.9	1.0 ± 0.8	.931
Initial eGFR, mL/min/1.73 m^2	86.4 ± 27.1	79.1 ± 21.6	.222
Follow-up eGFR, mL/min/1.73 m^2	82.9 ± 24.4	90.8 ± 21.1	.149
Change in eGFR, mL/min/1.73 m^2	-2.4 ± 15.1	10.4 ± 18.7	.001
Initial NT-proBNP, pg/mL	289.0 [73.8, 1260.5]	1146.0 [91.0, 2220.0]	.194
Follow-up NT-proBNP, pg/mL	62.0 [37.0, 192.5]	41.0 [21.2, 107.2]	.239
Change in NT-proBNP, pg/mL	-82.5 [-609.0, -0.8]	-622.0 [-1515.5, -28.8]	.063
Initial hemoglobin, g/dL	11.3 ± 2.5	13.8 ± 1.9	<.001
Follow-up hemoglobin, g/dL	12.1 ± 2.2	13.4 ± 1.6	.004
Change in hemoglobin, g/dL	0.6 ± 2.3	-0.3 ± 1.7	.048
Symptoms at follow-up	25 (30.9)	7 (28.0)	.981
Presence of RV dysfunction initial	40 (48.2)	23 (92.0)	<.001
Presence of RV dysfunction follow-up	24 (28.9)	7 (28.0)	>.99
Normalization of RV function	22 (26.5)	16 (64.0)	.001
Presence of any perfusion defects	15 (33.3)	6 (46.2)	.603
6-minute walk test distance, m	358.0 ± 98.9	358.2 ± 114.7	.994
Median days to clinic follow-up	121.0 [96.5, 179.5]	163.0 [122.0, 215.0]	.056

Values are mean ± SD, n (%), or median [IQR].
eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal proB-type natriuretic peptide; PESI, pulmonary embolism severity index; RV, right ventricular; sPESI, simplified PESI.

bleeding risk, failed systemic thrombolysis, or are at risk of death within hours.[22]

Our study extends the previous findings that EVT improves RV dilation by demonstrating prolonged normalization of RV size or function at a median of 120 days after diagnosis. The normalization of RV function was significantly greater in patients treated with EVT plus medical therapy compared with those treated using medical therapy alone. We found that 71% of patients treated with EVT had normalization of RV function at follow-up. These results are similar to a recent retrospective study of 81 patients with intermediate to high risk PE treated with EVT, which found that 62% of patients with follow-up TTE had return to normal RV function at a median of 58 days.[23] In our study, nearly all patients classified as increased risk (defined as ESC risk class of intermediate-high or high) had evidence of RV dysfunction at baseline. While 76% of these higher-risk patients who were treated with EVT experienced a normalization of their RV function at follow-up, only 57% of medically treated patients had full recovery of RV function. Further, our study demonstrated that the normalization of RV function was seen across ESC and PESI risk groups, including ESC low risk, PESI class I (very low risk), and PESI class II (low risk) groups. Even among this low risk cohort, 64% of patients who had received EVT had normalization of RV function at follow-up compared to only 27% of patients who had been treated with medical therapy alone (Table 3, Supplemental Table S1).

In addition to assessing improvements in imaging and laboratory data, our study assessed quality-of-life measures at follow-up including presence of patient reported symptoms as well as 6MWD. Among the entire cohort at follow-up, there was no significant difference in either metric between patients who received EVT vs medical therapy. However, among patients considered intermediate-high and high risk by the ESC guidelines, those treated with EVT had significantly greater 6MWD compared with those treated with medical therapy alone ($P = .025$). This



Central Illustration.
Follow-up of patients with acute pulmonary embolisms who recieved endovascular and medical therapy showed improvement in eGFR, improvement in normalization of right ventricular function, and decrease in hemoglobin compared to medical therapy alone. eGFR, estimated glomerular filtration rate; RV, right ventricle.

finding was also observed in patients with intermediate to high risk PESI scores with a trend toward increased 6MWD in those treated with EVT ($P = .058$, Supplemental Table S1). Interestingly, we observed that intermediate-high and high risk patients treated with medical therapy alone had the lowest distance achieved on 6-minute of any group (Table 3). There was no significant difference in 6MWD between EVT and medical therapy groups in intermediate-low and low risk patients (Table 3). The addition of quality-of-life metrics to traditional clinical end points in future trials, such as the Ultrasound-facilitated, Catheter-directed, Thrombolysis in Intermediate-high Risk Pulmonary Embolism (HI-PEITHO) and the Pulmonary Embolism: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (PE-TRACT), will be of great clinical interest. Lastly, it is worth mentioning that only one patient who received EVT was classified as low risk by the ESC guidelines. This is compared with 25 (45.5%) patients who received EVT who were classified as low risk by PESI score. The incongruity in risk stratification observed in our study highlights the differences of these 2 models. Young patients, due to the inclusion of age as an important component of the PESI score, may have an underestimated risk.

There remains much interest in the rates of CTEPH following acute PE. The true incidence of CTEPH after PE is controversial; however, estimates somewhere between 1% to 5% are generally accepted.[24] We assessed all patients for the presence of any perfusion defects on V/Q scintigraphy, the first-line diagnostic test for the diagnosis of CTEPH following acute PE.[18] A large number (~50%) of patients in both groups had some perfusion defect(s) at follow-up, although there was no difference between patients receiving EVT and those treated with medical therapy alone. When comparing the type of technique used for EVT (ie: catheter-directed thrombolytics vs mechanical thrombectomy), over 90% of patients who received mechanical thrombectomy had presence of perfusion defects on V/Q scan compared with only 42% of patients who received catheter-directed thrombolytics (Supplemental Table S4). While the results are intriguing and hypothesis generating, this finding should be interpreted with caution given the small numbers. Further work is needed to accurately characterize the incidence rates of CTEPH following acute PE, determine the clinical significance of residual pulmonary vascular occlusion, and further compare the incidence rates of CTEPH in patients treated with EVT versus medical therapy alone across risk strata and EVT types.

It is worth noting that 24 (41%) patients who received EVT were categorized as intermediate-low risk by the 2019 ESC guidelines. We hypothesize multiple reasons for this finding. First, 75% of the patients in this group presented prior to the release of the 2019 ESC guidelines. Second, the ESC risk stratification model does not consider degree of hypoxia, patient wishes or values, or the severity symptoms, all of which likely influence the decision to pursue EVT. Third, our study included both traditional troponin (prior to institutional change) and high-sensitivity troponin values. It is possible that traditional troponin values were not sensitive enough to diagnose subtle elevations (below 30 ng/L), which may have been detected on newer high-sensitivity troponin assays and used in clinical decision making.

The clinical significance of the greater decrease in hemoglobin values in patients treated with EVT is unclear. It is possible that higher baseline hemoglobin levels were preferred in the selection of patients appropriate for EVT. Given that at follow-up there was no difference in hemoglobin levels between the EVT and medical therapy alone groups, the true impact of this change is likely minimal.

Our study is one of the first to compare the benefits of EVT plus medical therapy to medical therapy alone in patients with extensive follow-up data up to 6 months. However, the results of our study should be interpreted in the context of its limitations. First, this study was conducted in a retrospective manner at a single institution. We only included patients who returned for their outpatient follow-up visits. As a result, patients who were likely extremely high risk (ie, those who died in the hospital or who were too ill to return to clinic) were excluded from analysis. Nonsignificant findings should be interpreted with caution given our relatively small cohort. Further, as 398 patients did not present for their 3 to 6 month follow-up visits, we cannot exclude the possibility of selection bias. Additionally, while patients were recommended for 6-minute walk test and V/Q scan based on the presence of symptoms, there was a high percentage of patients who did not complete testing (45.8% for 6-minute walk and 39.5% for V/Q scan). Finally, this trial was conducted at a single center with a mature PERT program and a group of experienced operators. These features may not be

generalizable to a larger population. Further understanding of the long-term risks and benefits of EVT with multicenter, prospective, randomized trials is needed. The results from the HI-PEITHO and PE-TRACT trials will hopefully provide much needed guidance.

Conclusions

Patients with acute PE who received EVT plus medical therapy were more likely to achieve normalization of RV function at 3 to 6 month follow-up compared with patients who received medical therapy alone, and this difference was especially pronounced in intermediate-high and high risk patients. At the time of PE diagnosis, patients receiving EVT had higher NT-proBNP and lower eGFR values but experienced statistically significant improvement in these variables at follow-up to levels superior to those treated medically. These data suggest that EVT is an effective therapy option for acute PE in intermediate-high and high risk patients with potential durable long-term benefits.

Declaration of competing interest

Dr Paul received research grants from Inari Medical, consulting fees from Argon Medical, and has equity in Flow Medical. Dr Ahmed is on the advisory board for Medtronic, Argon, Boston Scientific, and Johnson and Johnson and received consultant fees from Angiodynamics, Asahi, Canon, Philips, Cook, Varian, speaker honoraria from Penumbra, and research grants from Canon. Dr Bag received research grants from United Therapeutics, Medtronic, Reata Pharmaceuticals, Gilead, Liquidia, PhaseBio, Actelion, and Bayer and received speaker and consultant honoraria from Bayer. All other authors have no relevant disclosures.

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Ethics statement and patient consent

The research reported has adhered to the relevant ethical guidelines. Patient consent has been obtained, if needed. The institutional review board at the University of Chicago reviewed and approved the study (IRB16-0336).

Peer review statement

Given his role as Associate Editor, Sandeep Nathan had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Associate Editor Sahil A. Parikh.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2023.100602.

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