JAMA Cardiology | Original Investigation

Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High–risk Pulmonary Embolism
The CANARY Randomized Clinical Trial

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IMPORTANCE The optimal treatment of intermediate-high–risk pulmonary embolism (PE) remains unknown.

OBJECTIVE To assess the effect of conventional catheter-directed thrombolysis (cCDT) plus anticoagulation vs anticoagulation monotherapy in improving echocardiographic measures of right ventricle (RV) to left ventricle (LV) ratio in acute intermediate-high–risk PE.

DESIGN, SETTING, AND PARTICIPANTS The Catheter-Directed Thrombolysis vs Anticoagulation in Patients with Acute Intermediate-High–Risk Pulmonary Embolism (CANARY) trial was an open-label, randomized clinical trial of patients with intermediate-high–risk PE, conducted in 2 large cardiovascular centers in Tehran, Iran, between December 22, 2018, through February 2, 2020.

INTERVENTIONS Patients were randomly assigned to cCDT (alteplase, 0.5 mg/catheter/h for 24 hours) plus heparin vs anticoagulation monotherapy.

MAIN OUTCOMES AND MEASURES The proportion of patients with a 3-month echocardiographic RV/LV ratio greater than 0.9, assessed by a core laboratory, was the primary outcome. The proportion of patients with an RV/LV ratio greater than 0.9 at 72 hours after randomization and the 3-month all-cause mortality were among secondary outcomes. Major bleeding (Bleeding Academic Research Consortium type 3 or 5) was the main safety outcome. A clinical events committee, masked to the treatment assignment, adjudicated clinical outcomes.

RESULTS The study was prematurely stopped due to the COVID-19 pandemic after recruiting 94 patients (mean [SD] age, 58.4 [2.5] years; 27 women [29%]), of whom 85 patients completed the 3-month echocardiographic follow-up. Overall, 2 of 46 patients (4.3%) in the cCDT group and 5 of 39 patients (12.8%) in the anticoagulation monotherapy group met the primary outcome (odds ratio [OR], 0.31; 95% CI, 0.06-1.69; $P = .24$). The median (IQR) 3-month RV/LV ratio was significantly lower with cCDT (0.7 [0.6-0.7]) than with anticoagulation (0.8 [0.7-0.9]); $P = .01$). An RV/LV ratio greater than 0.9 at 72 hours after randomization was observed in fewer patients treated with cCDT (13 of 48 [27.0%]) than anticoagulation (24 of 46 [52.1%]; OR, 0.34; 95% CI, 0.14-0.80; $P = .01$). Fewer patients assigned to cCDT experienced a 3-month composite of death or RV/LV greater than 0.9 (2 of 48 [4.3%] vs 8 of 46 [17.3%]; OR, 0.20; 95% CI, 0.04-1.03; $P = .048$). One case of nonfatal major gastrointestinal bleeding occurred in the cCDT group.

CONCLUSIONS AND RELEVANCE This prematurely terminated randomized clinical trial of patients with intermediate-high–risk PE was hypothesis-generating for improvement in some efficacy outcomes and acceptable rate of major bleeding for cCDT compared with anticoagulation monotherapy and provided support for a definitive clinical outcomes trial.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05172115

Visual Abstract

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Supplemental content

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JAMA Cardiol. 2022;7(12):1189-1197. doi:10.1001/jamacardio.2022.3591
Published online October 19, 2022.

The role of reperfusion therapy in intermediate-risk pulmonary embolism (PE) is still debated. Patients with accompanying right ventricular (RV) dysfunction and/or elevated cardiac biomarkers have a higher risk for decompensation or death compared with patients who have lower-risk PE.[1] In the Pulmonary Embolism Thrombolysis (PEITHO) trial, full-dose systemic fibrinolytic therapy was tested in patients with intermediate-high-risk PE compared with anticoagulation monotherapy.[2] Although the risk of clinical deterioration was lower in patients treated with fibrinolytic therapy, the higher incidence of bleeding events counterbalanced the benefit.[2]

Catheter-directed thrombolysis (CDT) may optimize fibrinolytic drug delivery into the pulmonary arteries and consequently decrease the required dose, which may translate to fewer bleeding events. In prior observational studies and relatively small clinical trials of CDT, potentially beneficial effects were observed on short-term metrics, such as RV function.[3-6] However, it remains unknown whether there is a durable beneficial effect on improving RV function (lasting beyond short-term follow-up) for CDT compared with anticoagulation monotherapy. Accordingly, we compared the effect of conventional CDT (cCDT) plus anticoagulation vs anticoagulation monotherapy on decreasing the 3-month proportion of patients with an RV to left ventricle (LV) ratio (RV/LV) greater than 0.9 in patients with acute intermediate-high-risk PE.

Key Points

Question What are the effects of conventional catheter-directed thrombolysis (cCDT) plus anticoagulation in patients with acute intermediate-high–risk pulmonary embolism (PE)?

Findings In this prematurely terminated randomized clinical trial of 94 patients with intermediate-high–risk PE, cCDT compared with anticoagulation monotherapy did not significantly decrease the proportion of patients with a 3-month right ventricle to left ventricle ratio of greater than 0.9 but was associated with improvement in other imaging parameters. There was only 1 case of nonfatal major bleeding with cCDT.

Meaning The findings are encouraging for the design and execution of a definitive clinical outcomes trial.

Methods

Trial Oversight and Design

The Catheter-Directed Thrombolysis vs Anticoagulation Monotherapy in Patients With Acute Intermediate-High-Risk Pulmonary Embolism (CANARY) trial was an open-label, parallel-group, masked-end point, randomized clinical trial performed in 2 large cardiovascular centers in Tehran, Iran: the Rajaie Cardiovascular, Medical and Research Center and the Tehran Heart Center. The study protocol (Supplement 1) was approved by the ethics committee of the Rajaie Cardiovascular, Medical and Research Center and accepted by Tehran Heart Center. All patients provided written informed consent. An independent Data and Safety Monitoring Committee monitored the trial results. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Study Population

Adult patients (≥18 years) presenting within 14 days from symptom onset with acute intermediate-high-risk PE (according to the latest classification of the European Society of Cardiology guidelines at the time of trial design[7]), simplified PE severity index score of 1 or more,[8] and PE confirmation with computed tomography pulmonary angiography (CTPA) were considered for inclusion. Excluded from the study were patients with creatinine clearance less than 30 mL/min (to convert to milliliter per second per meter squared, multiply by 0.0167), contraindications to fibrinolytic therapy (such as history of intracranial bleeding or recent ischemic stroke), concomitant right heart thrombosis, or terminal illness. Information regarding patient race and ethnicity was not systematically gathered in this study. A full list of eligibility criteria can be found in Supplement 1.

Randomization and Treatment Strategy

Randomization was carried out in a 1:1 ratio to cCDT plus anticoagulation vs anticoagulation monotherapy via an electronic web-based system with permuted blocks of 4 and concealed allocation sequences. For the patients assigned to the anticoagulation monotherapy group, twice-daily subcutaneous enoxaparin (1 mg/kg) was started for the first 48 hours of enrollment.[9]

For patients assigned to cCDT, 1 infusion catheter was used per involved pulmonary artery, 1 in the left and 1 in the right pulmonary artery in case of bilateral involvement (Cragg-McNamara Valved Infusion Catheters; Medtronic). A fixed dose of alteplase (Actilyse; Boehringer Ingelheim) at a rate of 0.5 mg per catheter per hour for 24 hours (ie, a total of 12 mg for unilateral and 24 mg for bilateral involvement of pulmonary arteries, respectively) was administered. A fixed dose of unfractionated heparin (UFH; 500 units/hour) was administered to all the patients in the cCDT group during fibrinolytic therapy. After the termination of cCDT and removal of catheter(s), UFH was increased to therapeutic levels. Afterward, UFH was changed to twice-daily subcutaneous enoxaparin (1 mg/kg) in patients without procedural complication (eg, major vascular access complication or bleeding events) or unstable hemodynamics necessitating other invasive therapies. Enoxaparin was planned to be continued for the first 48 hours after completion of fibrinolytic therapy. For both groups, transition to oral anticoagulation was permissible at the discretion of treating clinicians. Details about the treatment strategy in each group can be found in Supplement 1.

Follow-up Clinical and Transthoracic Echocardiographic Examination

During the hospital course, every patient was monitored daily by the study team. A structured 3-month follow-up program was designed. The 3-month follow-up session was planned with detailed history taking, a transthoracic echocardiographic (TTE) examination, and a 6-minute walk test.

In the course of the trial, 3 TTE examinations were planned for each trial participant: on admission, 72 hours after randomization, and at the 3-month follow-up (Supplement 1). The first TTE was performed by the on-call cardiologist for risk stratification and investigation of eligibility criteria (eg, the presence of right heart thrombosis). The 2 subsequent TTE examinations (at 72 hours after randomization and at the 3-month follow-up) were recorded and sent to an imaging core laboratory, masked to treatment assignment. All the conventional measurements were performed based on the latest American Society of Echocardiography guidelines[10]; RV/LV ratio at 72 hours after randomization and at the 3-month follow-up was measured in the apical 4-chamber view. Three-month echocardiographic RV recovery was based on the PEITHO definition[11] as follows: (1) RV size (end-diastolic diameter measured at mid-RV in the RV-focused view) less than 35 mm, (2) pulmonary artery pressure less than 35 mm Hg (estimated from the highest tricuspid regurgitation gradient acquired from multiple views plus right atrial pressure based on inferior vena cava diameter and its respiratory collapse), (3) an RV/LV ratio less than 0.9, and (4) the normalization of RV free wall motion (in RV-focused view). The fulfillment of all the criteria, some criteria, and none of the criteria was defined as completely recovered, partially recovered, and unrecovered RV, respectively.[11] Additional details are summarized in Supplement 1.

Study Outcomes

The primary outcome was the proportion of patients with an RV/LV ratio greater than 0.9 at the 3-month follow-up assessed by the imaging core laboratory. Secondary outcomes included the proportion of patients with an RV/LV ratio greater than 0.9 at 72 hours after randomization and the proportion of patients with unrecovered RV at the 3-month follow-up and the 3-month rate of all-cause mortality.

Exploratory outcomes included a composite of the 3-month rate of all-cause mortality or the proportion of patients with an RV/LV ratio greater than 0.9 at the 3-month follow-up (ie, the primary outcome), 3-month rate of PE-related mortality, hospital length of stay (index hospitalization), and 6-minute walk test at 3-month follow-up. The main prespecified safety outcome was major bleeding based on the classification of the Bleeding Academic Research Consortium (BARC) (Supplement 1). BARC type 3 or 5 was considered as major bleeding.[12] Additional safety outcomes were severe thrombocytopenia (platelet count <20 × 10^3/μL; to convert to 10^9 thrombocytes/L, multiply by 1), vascular access complication, and clinically relevant nonmajor bleeding (BARC type 2). A clinical events committee, masked to the treatment assignment, adjudicated the clinical outcomes.

Statistical Analysis

Power calculation was performed for 2-sided superiority testing for the primary outcome in all the patients randomly assigned to treatment groups. Based on the pooled prevalence of RV dysfunction in the systematic review performed by Sista et al,[13] an 18.3% event rate for the primary outcome of an RV/LV ratio greater than 0.9 in the control group was presumed. Considering a 2-sided α of 0.05 and using the *z* approximation formula for comparing 2 proportions between independent groups, a sample size of 144 patients in each group (288 total) was calculated to reach a power of 80% for the detection of a 10% absolute risk reduction in the primary outcome with cCDT by comparison with anticoagulation monotherapy. However, midway through the conduct of the current study, in February 2020, the COVID-19 pandemic affected the study sites. Due to unprecedented strain on the health care system in the enrolling centers, which affected the care even for patients with non–COVID-19 venous thromboembolism,[14] the steering committee made the decision to stop patient recruitment on February 4, 2020. The primary outcome, unrecovered RV at the 3-month follow-up and the 6-minute walk test at the 3-month follow up, were analyzed in patients with valid values, ie, those who were alive and agreed to participate in the 3-month follow-up visit. Other outcomes were analyzed on all randomly assigned patients.

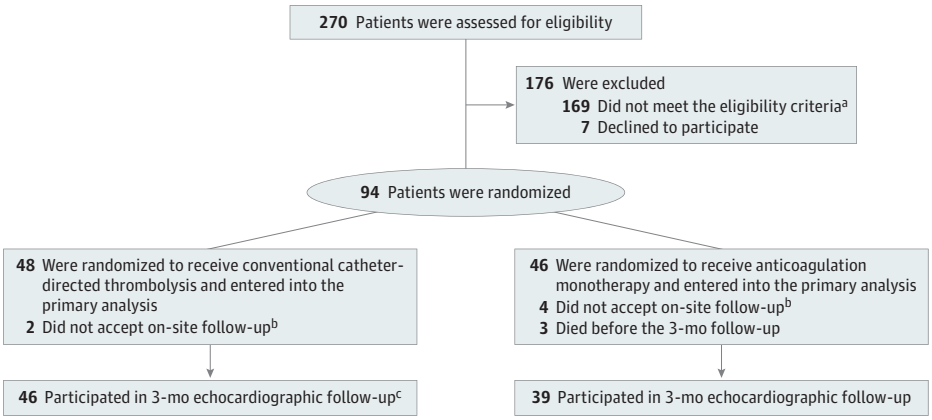
Categorical variables were expressed as frequencies with percentages. Continuous variables were described as the mean and SEM, if normal distribution was confirmed. The effect of the intervention on the outcomes was reported with odds ratio (OR) as the effect measure. A *P* value < .05 was considered significant for the primary outcome. Other *P* values were not adjusted for multiplicity of comparisons and should be considered exploratory.

After completion of enrollment but before completing the analyses of the trial data, it was planned to conduct a random-effect meta-analysis from the CDT groups of prior randomized trials plus the current trial with the goal of assessing pooled relative frequency of bleeding events (eMethods in Supplement 2). Subgroup analyses among the participants of the current trial were performed based on age, sex, body mass index (BMI; ≥30 or <30; calculated as weight in kilograms divided by height in meters squared), history of diabetes, hypertension, coronary artery disease, and heart rate on admission (≥110 or <110 beats/minute).

Results

From December 22, 2018, through February 2, 2020, a total of 270 patients were screened for eligibility. Overall, 94 patients were randomly assigned to the cCDT (48 [51%]) and control (46 [49%]) groups (mean [SD] age, 58.4 [2.5] years; 27 women [29%]; 67 men [71%]) (**Figure 1**). Six patients (6.3%)—2 patients assigned to cCDT and 4 patients assigned to the anticoagulation monotherapy—refused to participate in the onsite 3-month in-person follow-up required for the primary outcome due to difficulties imposed by the COVID-19 pandemic. However, these patients agreed to a phone interview to ascertain survival and symptoms. Three patients, all assigned to anticoagulation monotherapy, died before the 3-month follow-up. Consequently, from the initial 94 patients, 85 patients completed the 3-month echocardiographic follow-up, which was required for the primary outcome (eResults, eTables 1, 2, and 3 in Supplement 2).

Figure 1. Enrollment and Randomization



[a] Among 169 patients not meeting the eligibility criteria, 91, 48, and 11 patients were categorized as having low, intermediate-low, and high risk of developing pulmonary emboli. Ten patients had 1 or more contraindication to fibrinolytic therapy. Eight patients experienced end-stage kidney disease. One patient had allergy to iodine-based contrast.

[b] Six patients in the study (2 in the conventional catheter-directed thrombolysis group and 4 in the anticoagulation group) did not agree to participate in the 3-month on-site imaging follow-up, but they did agree to have off-site clinical follow-up assessment by phone interview.

[c] All images obtained from patients participating in the echocardiographic 3-month follow-up were considered acceptable by the core laboratory.

The 2 study groups were balanced in terms of baseline characteristics (**Table 1**).[15,16] Baseline RV/LV ratio greater than 0.9 was consistent between CTPA and bedside TTE at the time of enrollment in all patients. One patient with active cancer, assigned to anticoagulation monotherapy, was discharged with low-molecular-weight heparin; all other surviving patients were discharged with oral anticoagulation. Considering the bilateral involvement of the pulmonary arteries in all patients randomly assigned to cCDT, all patients were assigned to receive a fixed dose of alteplase, 24 mg, over 24 hours.

Efficacy Outcomes

At 3-month follow-up, the primary efficacy outcome (the proportion of patients with an RV/LV ratio >0.9 at 3-month follow-up) was not significantly different in the cCDT group compared with the anticoagulation monotherapy group (2 of 46 patients [4.3%] vs 5 of 39 patients [12.8%]; OR, 0.31; 95% CI, 0.06-1.69; P = .24) (**Table 2**). The median (IQR) RV/LV ratio at 3-month follow-up was significantly lower in the cCDT group compared with the anticoagulation monotherapy group (0.7 [0.6-0.7] vs 0.8 [0.7-0.9]; P = .01) (eFigure 1 in Supplement 2).

For the secondary efficacy outcomes, fewer patients assigned to cCDT had an RV/LV ratio greater than 0.9 at 72 hours after randomization (13 of 48 patients [27.0%]) compared with those assigned to anticoagulation monotherapy (24 of 46 patients [52.1%]; OR, 0.34; 95% CI, 0.14-0.80; P = .01). The median (IQR) RV/LV ratio was lower in the cCDT group at 72 hours after randomization (0.8 [0.7-0.9] vs 0.9 [0.8-1.1]; P = .001) (eFigure 1 in Supplement 2).

The rate of unrecovered RV function was lower at 3-month follow-up with cCDT compared with anticoagulation monotherapy (3 of 46 patients [6.2%] vs 11 of 39 patients [28.2%]; OR, 0.18; 95% CI, 0.06-0.77; P = .009) (Table 2). Clinical deterioration (ie, hemodynamic instability despite treatment with vasopressor agent) occurred in 1 of 46 patients (2.1%) in the anticoagulation monotherapy group. The patient subsequently received open-label cCDT as part of routine care. Patients in both groups had similar hospital lengths of stay (median [IQR], 6 [5-8] days; P = .45). All patients were discharged from the hospital alive.

Three patients died during the 3-month follow-up, all in the anticoagulation monotherapy group, of whom 2 events were adjudicated as PE-related mortality. For the third patient, PE-related death and cancer-related death were the 2 possible etiologies. However, the clinical events committee concluded that sufficient information was not available to ascertain the cause. A composite of 3-month mortality or having an RV/LV ratio greater than 0.9 at a 3-month follow-up was observed in 2 of 48 patients (4.3%) in the cCDT group and 8 of 46 patients (17.3%) in the anticoagulation monotherapy group (OR, 0.20; 95% CI, 0.04-1.03; P = .048) (Table 2). The TTE-based 3-month estimated pulmonary artery systolic pressure had reliable measurements according to the core laboratory in 79 patients (92%) and were not significantly different between the 2 groups (median [IQR], 30 [25-35] mm Hg vs 34 [27-45] mm Hg in the cCDT and anticoagulation monotherapy groups, respectively; P = .33).

Due to logistical limitations, the 6-minute walk test at 3-month follow-up was performed in only 1 of 2 enrolling centers (34 patients). There was no significant difference in the median (IQR) walk distance among patients randomly assigned to cCDT (415 [339-455] m) vs those randomized to standard anticoagulation (368 [270-442] m; P = .31).

Table 1. Baseline Characteristics in Patients Who Completed the 3-Month Follow-up[a]

Characteristic	No. (%)	
	cCDT + anticoagulation (n = 46)	Anticoagulation monotherapy (n = 39)
Age, mean (SEM), y	57.7 (2.2)	57.5 (2.4)
Sex		
Female	13 (28)	11 (28)
Male	33 (72)	28 (72)
Body mass index, mean (SEM)[b]	28.3 (0.7)	29.3 (1.0)
Vital signs on admission, mean (SEM)		
Systolic blood pressure, mm Hg	129.1 (3.3)	122.9 (2.6)
Heart rate, beats/min	102.6 (2.7)	105.0 (3.2)
Coexisting conditions		
Diabetes	6 (13)	9 (23)
Hypertension	13 (28)	14 (36)
Dyslipidemia	5 (11)	7 (18)
Coronary artery disease	8 (17)	8 (21)
Obstructive airway disease	2 (4)	3 (8)
Previous cerebrovascular accident	1 (2)	0
Previous history of PE	1 (2)	1 (2)
Active malignancy	0	0
Immobility ≥3 d	10 (23)	9 (22)
Surgery within prior 4 wk	3 (7)	3 (8)
Anemia[c]	6 (13)	5 (13)
Previous statin therapy	3 (7)	6 (15)
BACS bleeding score[d]		
Low risk	35 (76)	31 (79)
Intermediate risk	11 (23)	8 (20)
Baseline CTPA indices, mean (SEM)		
Right-to-left ventricle ratio[e]	1.2 (0.1)	1.2 (0.3)
Pulmonary artery obstruction index, %[f]	55.1 (1.4)	55.2 (1.2)
Baseline laboratory tests, mean (SEM)[g]		
High-sensitivity troponin, ng/L	169.9 (68.2)	168.1 (73.3)
NT-proBNP, pg/L	1804.2 (524.1)	1762.4 (792.6)

Abbreviations: cCDT, conventional catheter-directed thrombolysis, CTPA, computed tomography pulmonary angiogram, NT-proBNP, N-terminal-pro–brain natriuretic peptide; PE, pulmonary embolus.

SI conversion factor: To convert troponin to micrograms per liter, divide by 1000 and multiply by 1.

[a] Baseline characteristics were analyzed in 85 patients who were alive and participated in the 3-month follow-up visit (eTable 1 in Supplement 2).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Anemia defined as hemoglobin level less than 13 g/dL (130 g/L) in men and less than 12 g/dL (120 g/L) in nonpregnant women.

[d] The Bleeding Age Cancer Syncope (BACS) scoring system consists of recent major bleeding (3 points), age older than 75 years (1 point), active cancer (1 point), and syncope (1 point). A score of 0 signifies a low risk, 1 to 3 an intermediate risk, and greater than 3 a high risk.[15]

[e] Mean (SEM) baseline echocardiographic right-to-left ventricle ratio was 1.1 (0.2) and 1.1 (0.3) in CDT and anticoagulation monotherapy groups.

[f] Calculated based on Qanadli score.[16]

[g] Normal limit for highly sensitive troponin and NT-proBNP were less than 19 ng/L and 125 pg/L, respectively, for both sexes.

Safety Outcomes

One case of BARC type 3a major bleeding (nonfatal gastrointestinal bleeding) occurred in the cCDT group. Spontaneous intramural esophageal hematoma was noted during the final hour of fibrinolytic infusion and was managed conservatively. No fatal or intracranial bleeding occurred in either group. Three cases of minor bleeding (vascular access-site hematoma, BARC type 2) were reported in the intervention group. Two patients had superficial hematomas larger than 5 cm in the greatest diameter, and 1 patient had a superficial hematoma smaller than 5 cm in the greatest diameter; the hematomas resolved spontaneously. There were no cases of severe thrombocytopenia.

The pooled proportion estimate for fatal bleeding, intracranial hemorrhage, and major bleeding in the CDT group of randomized clinical trials—including Ultrasound-Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA),[4] Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Pulmonary Embolism (OPTALYSE-PE),[6] Standard vs Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism (SUNSET-PE),[3] and CANARY—was estimated at 0.02% (95% CI, 0-1.15%), 0.44% (95% CI, 0-2.17%), and 1.76% (95% CI, 0.20%-4.27%), respectively (eFigure 2 in Supplement 2). No statistically significant heterogeneity was observed between CDT groups of these controlled trials regarding major bleeding (P value for Q = 0.39; I^2 = 5.52%), intracranial hemorrhage (P value for Q = 0.67; I^2 = 0.01%), or fatal bleeding (P value for Q = 0.91; I^2 = 0) (eFigure 2 in Supplement 2). The CDT protocols of these trials are summarized in eTable 2 in Supplement 2. Subgroup analysis did not show significant treatment interaction for the primary outcome in prespecified subgroups (**Figure 2**).

Discussion

In this randomized clinical trial of 94 patients with acute intermediate-high-risk PE, we observed numerically fewer patients who had an RV/LV ratio greater than 0.9 at 3-month follow-up with cCDT compared with those in the anticoagulation monotherapy group. In addition, cCDT was associated with lower median 72-hour and 3-month RV/LV ratios, a decrease in the proportion of patients with an RV/LV ratio greater than 0.9 at 72 hours after randomization, and a decrease in the number of patients with an unrecovered RV at 3-month follow-up. cCDT resulted in low major bleeding events (ie, only a single nonfatal gastrointestinal major bleeding event) compared with anticoagulation monotherapy. Three patients, all assigned to the anticoagulation monotherapy group, died during the study follow-up; 2 deaths were adjudicated to be caused by PE.

One of the major drawbacks of systemic fibrinolysis is major bleeding, which is related to the dose of fibrinolytic agent and administration over a short period of time. The markedly smaller dose of fibrinolytic agents with cCDT in the current study resulted only in 1 major bleeding event (2%), and no fatal or intracranial hemorrhage. Similarly, the dose of fibrinolytic agents in all other major RCTs on CDT has been at least 4-fold smaller than the standard dosage of systemic fibrinolytic therapy. Based on pooled analyses that were performed as a part of the current study, fatal and intracranial bleeding event rates were less than 1% with

Table 2. Study Outcomes in the Study Population

Outcome	No. (%)		Odds ratio (95% CI)	Risk ratio (95% CI)	*P* value[a]
	cCDT + anticoagulation	Anticoagulation monotherapy			
Primary outcome[b]					
3-mo Echocardiographic RV/LV ratio >0.9	2/46 (4.3)	5/39 (12.8)	OR, 0.31 (0.06 to 1.69)	0.33 (0.07 to 1.65)	.24
Other efficacy outcomes					
72-h RV/LV ratio >0.9[c]	13/48 (27.0)	24/46 (52.1)	OR, 0.34 (0.14 to 0.80)	0.52 (0.30 to 0.89)	.01
3-mo Unrecovered RV[b,d]	3/46 (6.2)	11/39 (28.2)	OR, 0.18 (0.06 to 0.77)	0.23 (0.07 to 0.770)	.009
3-mo All-cause mortality[c]	0/48	3/46 (6.5)	−6.50 (−13.06 to 6.14)		.40
Composite of 3-mo all-cause mortality or the primary outcome	2/48 (4.2)	8/46 (17.3)	OR, 0.20 (0.04 to 1.03)	0.24 (0.05 to 1.07)	.048
PE-related mortality[c]	0[e]	2/46 (4.3)	−4.35 (−11.34 to 2.66)	0.34 (0.07 to 1.65)	.34
Hospital length of stay, median (IQR), d[c]	6 (5-8)	6 (5-8)	NA	NA	.45
3-mo 6-min Walk test, median (IQR), m[f]	415 (339-455)	368 (270-442)	NA	NA	.31
Safety outcomes[c]					
BARC type 3 or 5	1/48 (2.1)	0	2.1 (−1.9 to 6.52)	NA	.86
CRNMB	3/48 (6.2)	0[e]	6.25 (−1.53 to 14.03)		.43
Major or nonmajor bleeding	4/48 (8.3)	0[e]	8.33 (−0.27 to 16.94)		.27
Vascular access complication	3/48 (6.2)	0[e]	6.25 (−1.53 to 14.03)		.43
Severe thrombocytopenia[h]	0	0	NA		NA

Abbreviations: BARC, Bleeding Academic Research Consortium; cCDT, conventional catheter-directed thrombolysis, CRNMB, clinically relevant nonmajor bleeding; LV, left ventricle; NA, not applicable; PE, pulmonary embolism; RV, right ventricle.

[a] Apart from primary outcome, other *P* values are exploratory. *P* values are calculated by Pearson χ^2 tests, or exact test, as needed.

[b] Primary outcome (3-month RV/LV ratio >0.9) and unrecovered RV, were analyzed in 85 patients (46 and 39 patients in CDT and anticoagulation monotherapy groups, respectively) who were alive and participated in the 3-month follow-up visit. Three patients died within 3 months, and 6 patients responded to the telephone follow-up but did not agree to proceed to the visit.

[c] Assessed in all 94 randomly assigned patients.

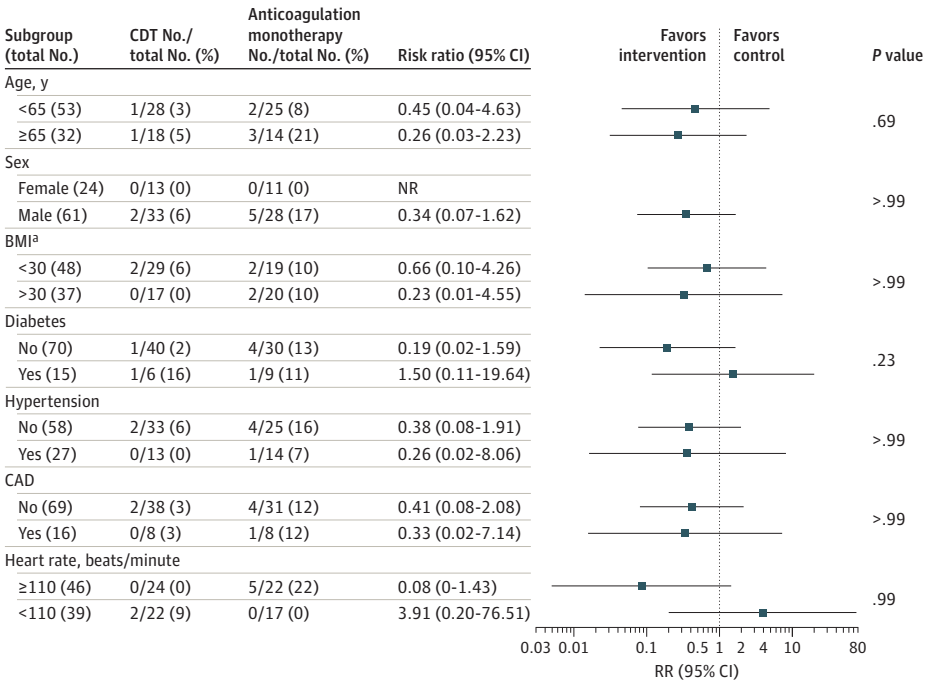
[d] The Pulmonary Embolism Thrombolysis (PEITHO) definition for echocardiographic RV recovery was used as follows: (1) RV size (in the modified 4-chamber view) less than 35 mm, (2) pulmonary artery pressure less than 35 mm Hg, (3) an RV/LV ratio less than 0.9, and (4) the normalization of RV free wall motion. The fulfillment of all the criteria, some criteria, and none of the criteria was defined as complete, partial, and no recovery, respectively.

[e] For events with 0 incidence in 1 group, only absolute risk difference was reported.

[f] Six-minute walk test was only evaluated in 1 center and tested in patients who participated in the follow-up visit and were able to exercise (14 patients in the CDT group and 20 patients in the anticoagulation-monotherapy group).

[g] Defined as platelet counts less than 20 × 10^3/μL (20 × 10^9/L).

Figure 2. Subgroup Analysis for the Primary Outcome



BMI indicates body mass index; CAD, coronary artery disease; CDT, catheter-directed thrombolysis; NR, not reported; RR, risk ratio.

[a] BMI calculated as weight in kilograms divided by height in meters squared.

CDT. The pooled estimate for major bleeding is 1.76%, compared with pooled major bleeding event rate of 7.7% for systemic fibrinolysis reported in prior analyses.[17] In the ongoing Ultrasound-Facilitated, Catheter-Directed, Thrombolysis in Intermediate-High-Risk Pulmonary Embolism (HI-PEITHO) trial, ultrasonography-assisted CDT and anticoagulation monotherapy will be compared in patients with intermediate-high-risk PE for a primary composite outcome of 7-day PE-related mortality, cardiorespiratory collapse, and recurrent PE.[18] Considerations for lower doses of fibrinolytic therapy have been made in observational studies,[19] and small trials of systemic fibrinolysis, as well.[20] The ongoing Pulmonary Embolism International Thrombolysis Study 3 (PEITHO-3) trial will compare reduced-dose systemic fibrinolytic therapy with anticoagulation monotherapy in patients with intermediate-high-risk PE.[21]

In the current study, compared with anticoagulation monotherapy, fewer patients treated with cCDT had an RV/LV ratio greater than 0.9 in 72 hours after randomization. Further, the 72 hours after randomization and 3-month median RV/LV ratio were smaller in patients treated by cCDT. It is known that patients receiving anticoagulant monotherapy have late catch-up improvement in the imaging markers of PE over time.[22,23] In addition, the median RV/LV ratio in both groups in the current trial were within normal range at 3-month follow-up. Nevertheless, prior investigations have suggested a progressive association between the increase in echocardiographic-based RV/LV ratio value and short- and long-term mortality.[24] The current study suggests a more favorable durable effect for cCDT compared with anticoagulation monotherapy on several 3-month imaging indices. Future RCTs should determine whether such hypothesis-generating imaging changes translate to relevant improvement in clinical outcomes.

The choice of the study intervention in the current trial deserves some discussion. Most available trials of CDT that have shown improvement in short-term imaging metrics, such as reduction in the RV/LV ratio[3,4,6] or computed tomography-based thrombus burden,[3] used ultrasound-assisted CDT vs anticoagulation monotherapy. The selection of cCDT in the current trial was due to higher cost and limited availability of ultrasound-assisted CDT in the study centers. Recently, the SUNSET-PE trial did not report a significant difference in the degree of thrombus resolution 48 hours after intervention with ultrasound-assisted CDT compared with cCDT.[3] Of note, the current study did not aim to compare the 2 modalities, and further studies in this regard are needed.

Limitations

The present study has several limitations. First, due to logistic restriction imposed by the pandemic, we prematurely discontinued the study, which made the trial underpowered for the prespecified primary outcome. Although this remains an important limitation, findings from the primary outcome and several secondary and exploratory analyses suggest favorable outcomes with cCDT compared with anticoagulation monotherapy, which should be verified in large trials. Second, the assessment of exercise capacity by the 6-minute walk test was performed in only half the patients. Future studies should assess such functional metrics, as well as quality of life in an adequately powered group of patients. Third, at the time of analysis, we recognized that women were underrepresented in our study (approximately 30%). Both enrolling centers are tertiary cardiovascular centers, accepting a high volume of referral patients. A careful assessment of the referred patients for screening indicated that 86 of 270 screened patients (32%) were female. The trial was offered similarly to women and men, and the rate of participation was also similar. We cannot exclude the possibility of chance alone but remain vigilant for our future randomized investigations. Additional studies are needed to understand whether intermediate-high-risk PE is more common among men in Iran or if disparities exist in treatment or referral to tertiary care centers. Fourth, only 2 patients had a prior history of PE. However, the relative frequency of previously undiagnosed chronic thromboembolic pulmonary hypertension in these patients is uncertain. Fifth, the assigned dosage of alteplase in the current study was based on available evidence at the time of trial design and is higher than a few more recently published or ongoing trials (eTable 2 in Supplement 2) in which a lower dose of alteplase per pulmonary artery has been considered. Finally, the majority of our study population had low baseline bleeding risk. Careful patient selection is always needed to consider the treatment tradeoffs of fibrinolytic therapy, including CDT.

Conclusions

To conclude, in the setting of premature termination, this randomized clinical trial was underpowered to detect a statistically significant difference between cCDT and anticoagulation monotherapy with regard to its primary outcome of proportion of patients with a 3-month RV/LV ratio of greater than 0.9. However, results suggest a hypothesis-generating improvement in secondary and exploratory outcomes, such as short-term and 3-month echocardiographic RV recovery, with cCDT compared with anticoagulation and also a low risk of major bleeding in patients treated with cCDT. These results are encouraging for the design and execution of a definitive outcomes trial. Results from the ongoing HI-PEITHO, PEITHO-3, PE-TRACT, and nonfibrinolysis mechanical-thrombectomy trials will be similarly enlightening for assessment of other treatment alternatives for intermediate-high-risk PE.

ARTICLE INFORMATION

Accepted for Publication: July 22, 2022.

Published Online: October 19, 2022. doi:10.1001/jamacardio.2022.3591

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Obtained funding: Sadeghipour, Shirani, Alizadehasl, Shafe.
Administrative, technical, or material support: Sadeghipour, Moosavi, Mohebbi, Pouraliakbar, Alizadehasl, Shafe, Giri, Piazza, Bikdeli.
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Conflict of Interest Disclosures: Dr Shishehbor reported receiving grants from Inari; personal fees from Boston Scientific, Abbott VAscular, Philips, and Terumo; and equity from Advanced Nano Therapies and Inquis Medical outside the submitted work. Dr Giri reported receiving personal fees from Inari, Boston Scientific, and Abiomed and grants from Inari, Boston Scientific, Abiomed, and the National Heart, Lung, and Blood Institute outside the submitted work. Dr Monreal reported receiving personal fees from Sanofi and grants from Sanofi, Rovi Pharmaceuticals, and Leo Pharma outside the submitted work. Dr Jimenez reported receiving personal fees from Bristol Myers Squibb, Pfizer, Sanofi, Leo Pharma, and Rovi Pharmaceuticals and grants from Daiichi-Sankyo, outside the submitted work; Dr Jimenez reported being a member of the steering committee of Pulmonary Embolism International Thrombolysis Study 3 (PEITHO-3) trial. Dr Lang reported receiving grants from Janssen and AOPHealth during the conduct of the study and personal fees from Janssen, AOPHealth, MSD Pharma Services, and Sanofi outside the submitted work. Dr Goldhaber reported receiving grants from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Boston Scientific, Daiichi-Sankyo, Janssen, the National Heart, Lung, and Blood Institute, the Thrombosis Research Institute, and Pfizer, and consulting fees Bayer, Agile, Boston Scientific, Boehringer Ingelheim, and Pfizer outside the submitted work. Dr Krumholz reported receiving personal fees from UnitedHealth, IBM, Watson Health, Aetna, Facebook, Element Science, Aetna, Reality Labs, F-Prime, Tesseract/4Catalyst, Martin/Baughman Law Firm, Arnold and Porter Law Firm, Siegfried and Jensen Law Firm, the National Center for Cardiovascular Diseases, Beijing, China, and the Massachusetts Medical Society (as coeditor of *Journal Watch Cardiology*); being a cofounder of HugoHealth, Refactor Health; having contracts with the US Centers for Medicare & Medicaid Services Association; grants from Medtronic, the US Food and Drug Administration, Johnson & Johnson, Bristol Myers Squibb/Pfizer, Janssen, Boston Scientific, Bayer, Alexion, Amgen, and the Shenzhen Center for Health Information; and consulting fees from Amgen, BSC, Janssen, Bristol Myers Squibb/Pfizer outside the submitted work. Dr Bikdeli reported receiving research support from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital, a Career Development Award by the American Heart Association, and VIVA Physicians; and being a consulting expert, on behalf of the plaintiff, for litigation related to 2 specific brand models of inferior vena cava filters. No other disclosures were reported.

Funding/Support: The study was supported by grants from Rajaie Cardiovascular Medical and Research Center and the Tehran Heart Center.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank Marjan Parvizi, BA (Tehran Heart Center), Nasim Jafari, BA, Maryam Zarinsadaf, BA, and Sara Tayyebi, MS (Rajaie Cardiovascular, Medical and Research Center), for their support and contribution to the CANARY study. No one was financially compensated for their contribution.

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Invited Commentary

Catheter-Directed Treatment of Submassive Pulmonary Embolism—A Cautious Step Closer?

Elaine M. Hylek, MD, MPH

Thrombolytic therapy is recommended for patients with pulmonary embolism and hemodynamic compromise, as associated mortality rates are reported to be as high as 50% by 90 days.[1-3] However, use of thrombolytic therapy for intermediate-risk or submassive pulmonary embolism, defined by right ventricular dysfunction without hemodynamic compromise, remains controversial due to the high risk of bleeding, including intracranial bleeding, associated with this treatment.[2-4] Sadeghipour and colleagues[5] report results from the Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High–Risk Pulmonary Embolism (CANARY) randomized clinical trial. The trial was designed as an open-label randomized assessment of conventional catheter-directed thrombolysis (cCDT) plus anticoagulation vs anticoagulation monotherapy in improving echocardiographic measures, specifically the right ventricle to left ventricle (RV/LV) ratio, measured at 3 months. As noted by the investigators, the trial was stopped early due to enrollment challenges during the COVID-19 pandemic. Among the 94 patients recruited, 46 were randomized to receive catheter-directed alteplase. Primary outcome data were available for 85 of 94 randomized patients (90%). As noted, 2 of 46 patients (4.3%) in the cCDT group and 5 of 39 (12.8%) in the anticoagulation monotherapy group met the primary outcome (odds ratio [OR], 0.31; 95% CI, 0.06-1.69; $P = .24$). Fewer patients who were randomized to cCDT experienced a 3-month composite outcome of death or RV/LV greater than 0.9 (2 of 48 [4.3%] vs 8 of 46 [17.3%]; OR, 0.20; 95% CI, 0.04-1.03; $P = .048$). One case of nonfatal major gastrointestinal bleeding occurred in the cCDT group.

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For perspective, the Pulmonary Embolism Thrombolysis (PEITHO) trial[6] also studied fibrinolytic therapy in an intermediate-risk population defined by right ventricular dysfunction, positive troponin, and normal blood pressure. Using a double-blind trial design, patients were randomized to a single-bolus injection of tenecteplase plus standard heparin therapy vs standard anticoagulation monotherapy. The primary efficacy outcome was the composite of death from any cause or hemodynamic decompensation within 7 days after randomization. Of the 506 patients in the tenecteplase group, death or hemodynamic decompensation occurred in 13 (2.6%) compared to 28 of 499 patients (5.6%) in the standard treatment group (OR, 0.44; 95% CI, 0.23-0.87; $P = .02$). In the safety analysis, 10 patients in the tenecteplase group (2%) sustained a hemorrhagic stroke compared to 1 patient (0.2%) in the standard anticoagulation group ($P = .003$). Extracranial bleeding occurred in 32 patients (6.3%) in the tenecteplase group and 6 patients (1.2%) in the placebo group ($P < .001$). The PEITHO trial documented the efficacy of thrombolytic treatment and