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Ultrasound-Assisted Catheter-Directed Thrombolytic Therapy Vs. Anticoagulation in Acute Intermediate-High Risk Pulmonary Embolism: A Quasi-Experimental Study

ABSTRACT

Background: Given the bleeding risk associated with full-dose intravenous thrombolytic treatment and the absence of randomized clinical trial evidence, current guidelines do not recommend reperfusion treatments as first-line therapy for intermediate-high risk (IHR) pulmonary embolism (PE). The aim of this study was to evaluate the effectiveness and safety of ultrasound-assisted catheter-directed thrombolysis (USAT) compared to anticoagulation therapy alone in patients with IHR PE.

Methods: A total of 425 patients diagnosed with acute PE and determined as IHR, 203 of whom underwent USAT, and 222 patients receiving only anticoagulants as the control group, were included. Baseline and post-treatment right ventricle (RV) function in echocardiography, tomographic RV/left ventricle (RV/LV) ratio, Qanadli score (Qs), and % changes from baseline were taken as primary effectiveness outcomes. For safety outcomes, major and minor bleeding and in-hospital all-cause death were adopted. Propensity score analysis was performed to reduce confounders and bias.

Results: The USAT treatment was found to be associated with improved RV function and decreased Qs, but no significant effect was observed on the RV/LV ratio and its change. Bleeding events were more frequent in the USAT group ($P < .001$ for both), and no difference was observed in terms of mortality.

Conclusion: The study, based on real-life data, has shown that a moderate-dose, slow-infusion tissue-type plasminogen activator regimen is superior to anticoagulant therapy alone in terms of reducing pulmonary arterial thrombus burden, restoring RV dysfunction, and improving clinical outcomes in acute PE patients at IHR. However, it has also resulted in a slight increase in bleeding events.

Keywords: Catheter directed thrombolytic therapy, pulmonary embolism, thrombolysis

INTRODUCTION

Despite recent advancements in prevention, diagnosis, and anticoagulant treatment, acute pulmonary embolism (PE) continues to be a major cause of global morbidity and mortality.[1,2] Recently, percutaneous catheter-directed treatment (CDT) has gained prominence as an alternative to anticoagulation, systemic thrombolytic treatment (STT), and surgical embolectomy, owing to its potential advantages and reduced risks. It provides a minimally invasive treatment option for acute PE patients when STT has failed or is contraindicated.[3] These endovascular techniques involve mechanically fragmenting, dispersing, or removing an obstructive thrombus, or administering locally low-dose thrombolytic agents with a lower risk of bleeding compared to STT.[4] Given the well-documented risks of bleeding with full-dose STT treatment and the absence of robust data regarding the clinical benefits of alternative reperfusion strategies, current guidelines do not recommend either STT or any other reperfusion therapy as first-line treatment for intermediate-risk PE.[1] Evidence from randomized controlled trials comparing these approaches with anticoagulant therapy, which supports their efficacy and safety, remains insufficient and also lacks reflection of real-world

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data. The study aimed to evaluate the effectiveness and safety of ultrasound-assisted catheter-directed thrombolysis (USAT), a percutaneous CDT method, in acute PE patients with intermediate-high risk (IHR), compared to anticoagulant therapy alone.

METHODS

Study Design and Population

A total of 425 patients out of 946 patients diagnosed with acute PE in the tertiary cardiovascular center between October 2012 and April 2023 were included, with 203 of them undergoing USAT and 222 receiving only anticoagulants as the control group. The systematic work-up for the initial diagnosis of acute PE and risk stratification, including multidetector contrast-enhanced computed tomography (CT) angiography, echocardiography assessments, PE severity indexes (PESI), and biomarker evaluation, was based on the criteria recommended by the ESC/ERS 2014 and 2019 PE guidelines, and all patients were at IHR.[1,5] The high-risk group and patients who underwent STT, those who received a different CDT other than USAT, those with symptom onset longer than 14 days, and those with the following contraindications for thrombolytics were excluded: hemorrhagic stroke or stroke of unknown cause at any time, ischemic stroke within the last 6 months, central nervous system damage or malignancy, gastrointestinal bleeding within the last month, known bleeding diathesis. Patients with a history of major trauma, bone fracture, or major surgery within the last 3 weeks, who constitute the high bleeding risk group, were not excluded from the study. Subsequently, these patients at IHR were divided into 2 groups: those receiving only anticoagulant therapy and those undergoing USAT. A total of 425 patients meeting the inclusion criteria were included in the study, with 222 patients receiving only anticoagulant therapy and 203 patients undergoing USAT. In all patients within the anticoagulant group, intravenous heparin was used, and the target activated partial thromboplastin time (aPTT) range was maintained between 50 and 75 seconds. The study protocol was approved by the Institutional Ethics Committee [no. 2023/07/687].

Chest Computed Tomography Pulmonary Angiography and Echocardiography

Computed tomography images were acquired using 64-slice helical CT angiography (Toshiba Aquilion 64™, Toshiba Medical Systems Corp., Tokyo, Japan). A validated CT score for pulmonary arterial (PA) occlusion proposed by Qanadli et al.[6] [Qanadli score (QS)], right ventricle (RV) to left ventricle (LV) ratio, RV diameter, right atrial to left atrial diameter ratio (RA/LA ratio), and main, left, and right PA diameters were measured from CT images. Pulmonary infarction is defined as a peripheral wedge-shaped pulmonary consolidation in a hypoperfused segment of the lung. The CT images were evaluated at admission and 72-96 hours after the initiation of treatment. Transthoracic echocardiography (TTE) was performed on all patients on the first day of admission and repeated at discharge. Tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler (S') measurements were obtained to assess RV function in TTE, and estimated pulmonary artery pressures (PAPs) were calculated from the tricuspid regurgitation jet. All measurements and assessments were made in accordance with the American Society of Echocardiography guidelines.[7]

Righ Heart Catheterization, Pulmonary Angiography, and Ultrasound-Assisted Catheter-Directed Thrombolysis Procedure

Only the femoral venous route with a 6-French (F) sheath was used, and arterial puncture was avoided. A 6F multipurpose catheter was used for initial PA pressure measurements and selective angiograms. The EkoSonic Endovascular Device (EKOS, Bothell, Washington) was employed, which includes the Intelligent Drug Delivery Catheter (IDDC) and the MicroSonic Device (MSD) equipped with multiple small ultrasound transducers distributed across the treatment zone. A 0.035-inch hydrophilic guidewire was used to navigate through the thrombotic segment of the target pulmonary artery (PA). Once positioned safely within a large segmental PA, the multipurpose catheter was exchanged for the IDDC of the USAT system. After removing the guidewire, the MSD was inserted and advanced through the IDDC, then connected to the EkoSonic control unit. Recombinant tissue-type plasminogen activator (tPA) was used as the thrombolytic agent, with a continuous infusion of tPA based on the selected dose and duration, and saline coolant at 35 mL/h per catheter was initiated. The preferred treatment approach involved operator-driven selection of tPA dose and treatment duration on an individual basis, tailored to each patient's risk status and comorbidities. Approximately 4 hours after the completion of tPA delivery, the system catheters and sheath were removed under fluoroscopic control. Intravenous heparin was started after termination of the

HIGHLIGHTS

- This study investigates the effectiveness and safety of ultrasound-assisted catheter-directed thrombolysis (USAT) vs. anticoagulation alone in patients with intermediate-risk pulmonary embolism (PE), given the limited options for reperfusion therapies.
- A total of 425 patients diagnosed with intermediate-risk acute PE were included, with 203 receiving USAT and 222 receiving standard anticoagulant therapy. Propensity score analysis was performed to allow robust comparisons.
- The USAT group demonstrated significant improvements in right ventricular function, Qanadli score, heart rate, oxygen saturation, and pulmonary artery pressure compared to the anticoagulant-only group.
- While USAT showed benefits in thrombus reduction and right ventricle function, it was associated with higher rates of bleeding, including major (5.9% vs. 0.9%) and minor (9.4% vs. 1.4%) events compared to anticoagulant therapy.
- The findings suggest that while USAT offers superior outcomes in managing intermediate-risk PE, clinicians must weigh these benefits against the increased risk of bleeding when considering treatment options.

USAT procedure, and the aim was to keep the aPTT around 60 seconds.

Primary Measures of Effectiveness

As measures of treatment effectiveness, TAPSE and its change were assessed using TTE, while baseline and post-treatment RV/LV ratio, PA obstruction severity (Qs), and their changes from baseline were evaluated using CT.

Safety Measures

For safety endpoints, major and minor bleeding events, as well as in-hospital deaths from all causes, were recorded. Major bleeding was defined as overt hemorrhage associated with a fall in the hemoglobin level ≥2.0 g/dL or with transfusion of 2 units of packed red blood cells, or involvement of critical site bleeding including airway, intra-abdominal, intracranial, and other central nervous system bleeding, pericardial tamponade, hemothorax, and retroperitoneal hematoma. Clinically overt bleeding not fulfilling the criteria of major bleeding was classified as a minor bleeding complication.[8]

Statistical Analysis and Modelling

Normally distributed continuous data were expressed as mean and standard deviation values, whereas non-normally distributed data were expressed as medians and interquartile ranges, and categorical data were described as absolute and percentage values. Independent samples *t*-test and Mann–Whitney *U* test were used for comparisons of independent continuous data groups, and Pearson χ^2 or Fisher's exact tests were used for comparisons of categorical data groups. Wilcoxon signed-rank test and paired *t*-test were used to compare mean differences based on the data distribution. Due to the observational nature of the study, there are differences among variables between the 2 groups. To balance these differences, prevent potential confounders, and reduce bias, propensity score analysis (PSA) has been used. The PSA methods of "propensity score matching" (PSM) and "inverse probability weighting" (IPW) have been used. The selection of variables was determined based on differences between the 2 groups, previous studies, and expert opinions. In PSM, a caliper of 0.1 was used, the matching method was chosen as k-nearest neighbors, and 1:1 matching was performed without replacement. Balance diagnostics of baseline covariates between treated and untreated subjects before and after propensity scoring were presented in terms of absolute standardized mean differences. Variables used in the PSA were age, sex, history of malignancy, history of stroke, postoperative status, presentation with syncope, PESI score, baseline systolic blood pressure (SBP), pre-treatment Qs, pre-treatment RV/LV ratio, and echocardiographic PAPs. Since the IPW method was more successful in terms of covariate balance regarding absolute standardized differences, this method was preferred (Figure 1 and Supplementary figure 1). After balancing the variables between the treatment and control groups, multiple linear regression analysis was conducted using effectiveness outcomes such as RV/LV_2 and its change, Qs_2 and its change, and $TAPSE^2$ and its change. Details of the analysis for each outcome are given in Supplementary tables.

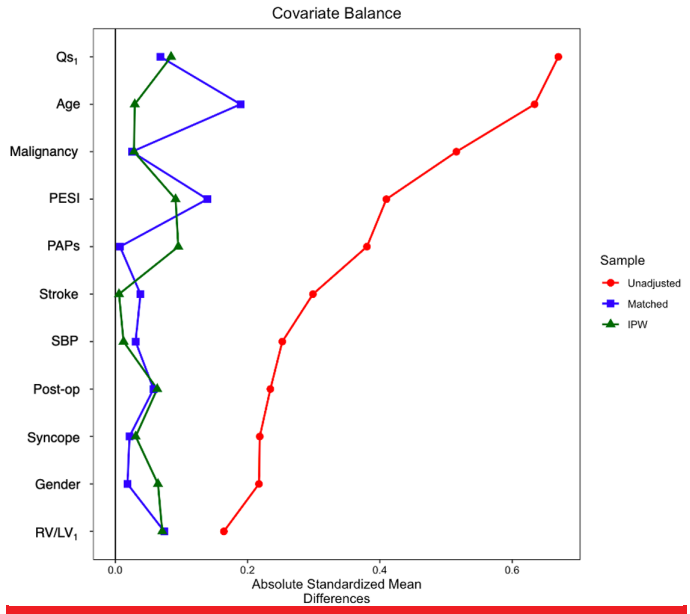

Figure 1. Comparison of variable balancing using PSM and IPW methods.

All baseline models included PESI and the RV/LV_1 ratio, while other variables were added based on previous studies, clinical experience, expert opinions, and variables found to be significant ($P < .05$) in simple linear regression analyses.

For all statistical analyses, 2-tailed probability (*P*) values of less than .05 were deemed to indicate statistical significance. All statistical analyses were performed using Jamovi and R 4.2 software (Vienna, Austria) with "Hmisc," "ipw," "matchit," "cobalt," and "rms" packages. During the preparation of this article, the authors did not use artificial intelligence-assisted technologies.

RESULTS

The baseline characteristics and clinical data of patients who underwent USAT and those who received only anticoagulants are presented in Table 1. The mean age of the USAT group was significantly lower than that of the anticoagulant group ($P < .001$). When examining comorbidities, medical history, and provoking factors, no significant differences were found between the 2 groups in terms of hypertension, diabetes, coronary artery disease, heart failure, hyperlipidemia, chronic obstructive pulmonary disease, atrial fibrillation, orthopedic surgery/fractures, oral contraceptive use, long travel, and thrombophilia. History of cerebrovascular events and malignancy was less common in the USAT group ($P = .003$ and $P < .001$ respectively). While there was no difference between the 2 groups regarding a history of venous thromboembolism, the incidence of acute deep vein thrombosis was higher in the USAT group ($P = .002$). Symptom duration, heart rate, and O_2 saturation did not differ between the 2 groups. Syncope at presentation was more common in the USAT group ($P = .025$). In vital signs, systolic blood pressure was lower in the USAT group ($P = .011$), and among prognostic markers, PESI, PESI Class, and simplified PESI were also lower in the USAT group ($P < .001$ for all). The imaging data of TTE

Table 1. Patients' Demographic, Clinical, and Laboratory Characteristics

	USAT n = 203	Anticoagulant n = 222	All Patients n = 425	*P*
Age, years	60.8 ± 15.9	70.5 ± 14.8	65.9 ± 16.1	<.001
Gender (male), n (%)	89 (43.8)	74 (33.3)	163 (38.3)	.026
Hypertension, n (%)	93 (45.8)	113 (50.9)	206 (48.5)	.274
Diabetes, n (%)	35 (17.2)	38 (17.1)	73 (17.2)	.990
CAD, n (%)	23 (11.3)	28 (12.6)	51 (12)	.672
Heart failure, n (%)	3 (1.5)	8 (3.6)	11 (2.6)	.166
Hyperlipidemia, n (%)	17 (8.4)	26 (11.7)	40 (10.1)	.248
COPD, n (%)	18 (8.9)	27 (12.2)	45 (10.6)	.263
Atrial fibrillation, n (%)	16 (7.9)	15 (6.7)	31 (7.3)	.665
Stroke, n (%)	5 (2.5)	21 (9.4)	26 (6.1)	.003
Past VTE, n (%)	19 (9.4)	19 (8.5)	38 (8.9)	.784
Acute DVT, n (%)	130 (64)	110 (49.5)	240 (56.5)	.002
Malignancy, n (%)	14 (6.9)	56 (25.2)	70 (16.5)	<.001
Postoperative status, n (%)	76 (37.4)	59 (26.6)	135 (31.8)	.016
Orthopedic surgery/fractures, n (%)	16 (7.9)	8 (3.6)	24 (5.6)	.056
HRT/OCS, n (%)	6 (3)	2 (0.9)	8 (1.9)	.058
Prolonged travelling, n (%)	17 (8.4)	9 (4)	26 (6.1)	.065
Thrombophilia, n (%)	3 (1.5)	1 (0.5)	4 (0.9)	.352
Syncope, n (%)	55 (27.1)	40 (18)	95 (22.3)	.025
Symptom duration, days	4 (2-7)	3 (2-7)	3 (2-7)	.097
SBP, mm Hg	123 ± 19.6	128 ± 20	126 ± 20	.011
DBP, mm Hg	78.1 ± 12.1	78.2 ± 14.8	78.2 ± 13.6	.608
Heart rate, /min	106 ± 16.9	108 ± 17.8	107 ± 17.4	.136
Oxygen saturation, %	88.9 ± 4.68	89.2 ± 5	89.1 ± 4.8	.663
PESI	98 (80.5-117)	106 (91-127)	102 (85-121)	<.001
PESI Class	3 (2-4)	4 (3-5)	3 (2-4)	<.001
sPESI	1 (1-2)	2 (1-2)	1 (1-2)	<.001
d-Dimer, mg/L	8 (4.6-15)	7.3 (4-14)	7.9 (4.1-14.7)	.408
Troponin, ng/mL	0.077 (0.04-0.235)	0.078 (0.043-0.230)	0.078 (0.04-0.236)	.583
CRP, mg/L	3.5 (1.9-8.1)	5.8 (2.1-14.8)	4.7 (2.1-11.8)	.026

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DBP, diastolic blood pressure; DVT, deep vein thrombosis; HRT/OCS, hormone replacement therapy/oral contraceptive drug; PESI, pulmonary embolism severity index; SBP, systolic blood pressure; USAT, ultrasound-assisted thrombolysis; VTE, venous thromboembolism.

and computed tomography pulmonary angiogram (CTPA) evaluations are presented in Table 2.

When admission RV function was assessed by TTE using TAPSE and S', no difference was found between the 2 groups. The estimated echocardiographic PAPs were higher in the USAT group ($P < .001$). Thrombus burden, as indicated by Qs, was higher in the USAT group ($P < .001$). While no difference was observed between the 2 groups in RV diameter and RV/LV_1 ratio, the RA/LA ratio was higher in the USAT group ($P = .001$). There was no significant difference between the 2 groups in terms of PA diameters, PA/Aorta ratio, presence of pleural effusion, and pulmonary infarction.

Catheter pressures, tPA duration and doses, and procedural details are presented in Supplementary Table 1. The majority of the procedures (82.9%) were bilateral. The mean infusion duration was 25.6 ± 6.6 hours. Post-procedural catheter-measured systolic, diastolic, and mean PAP showed a significant reduction compared to pre-procedural values ($P < .001$ for all).

Post-treatment clinical, echocardiographic, and tomographic measurements of the patients are summarized in Table 3. While no change was observed in SBP and DBP, the heart rate was lower and oxygen saturation was higher at discharge in the USAT group compared to those receiving anticoagulants ($P < .001$ and $P = .032$, respectively). Tricuspid annular plane systolic excursion, indicating RV function, was higher, and estimated PAPs were lower in the USAT group ($P = .007$ and $P = .016$, respectively). In tomographic measurements, Qs_2 indicating thrombus burden was significantly lower at discharge in the USAT group ($P < .001$), while no difference was found in the RV/LV_2 ratio. Although there was a significant reduction in the RA/LA_2 ratio compared to before treatment, the RA/LA_2 ratio remained high in the USAT group after treatment ($P < .001$). The presence of pleural effusion was equal in both groups, but pulmonary infarction was found to be more frequent in the USAT group ($P = .002$). Changes in clinical and imaging values before and after treatment for patients in both groups are summarized in Table 4. Changes

Table 2. Echocardiographic and Tomographic Measures

	USAT n = 203	Anticoagulant n = 222	All Patients n = 425	*P*
TAPSE, mm	18.2 ± 3.7	18.3 ± 4.3	1.8 ± 0.4	.716
S', cm/s	11.1 ± 2.3	12.1 ± 3.4	11 ± 2.9	.058
PAPs, mm Hg	55.6 ± 12.3	50.8 ± 12.9	53.2 ± 12.8	<.001
Qanadli score	23.7 ± 6.2	19 ± 5.9	21.4 ± 6.4	<.001
RV/LV_1 ratio	1.19 ± 0.19	1.23 ± 0.24	1.21 ± 0.21	.059
RV diameter, mm	43.7 ± 5.7	44.7 ± 6	44.3 ± 5.9	.125
RA/LA_1 ratio	1.35 ± 0.28	1.25 ± 0.22	1.3 ± 0.26	.001
Main PA diameter, mm	31 ± 4.16	30.2 ± 3.68	30.6 ± 3.94	.056
Left PA diameter, mm	23.1 ± 3.06	23.5 ± 2.7	23.3 ± 2.86	.246
Right PA diameter, mm	23.6 ± 3.42	24.3 ± 3.19	24 ± 3.3	.063
Main PA/Aorta ratio	0.91 ± 0.13	0.89 ± 0.13	0.9 ± 0.13	.147
Pleural effusion, n (%)	25 (12.3)	42 (18.9)	67 (15.8)	.135
Pulmonary infarction, n (%)	40 (19.7)	33 (14.9)	73 (17.2)	.246

LA, left atrium; LV, left ventricle; PA, pulmonary artery; PAPs, systolic pulmonary artery pressure; RA, right atrium; RV, right ventricle; S', right ventricle tissue doppler; TAPSE, tricuspid annular plane systolic excursion. 1, measurement at admission; 2, measurement after treatment.

in heart rate and oxygen saturation were greater in the USAT group compared to the anticoagulant group ($P = .007$ and $P = .015$, respectively) (Figure 2A and B). In echocardiographic data, changes in TAPSE and PABs were found to be higher in the USAT group (both $P < .001$) (Figure 2C and D). Significant difference in Qs after treatment was observed, while the amount of change in the RV/LV ratio remained the same ($P < .001$ and $P = .378$, respectively) (Figure 2E and F).

When examining the effect of variables on RV/LV change as an outcome, it was found that a higher baseline RV/LV_1 ratio was associated with an increase in change, while the PESI score was associated with a decrease in change ($P < .001$ and $P = .001$, respectively). When the RV/LV_2 ratio was taken as the outcome, only the RV/LV_1 ratio was found to be associated ($P = .001$). In both models, no association was found between USAT and the RV/LV ratio or its change.

As for the effect of variables on Qs change, it was found that a high pre-treatment Qs_1 and the application of USAT increased Qs change, while a history of heart failure reduced Qs change. For Qs_2, it was determined that a high Qs_1 was associated with an increase in Qs_2, while USAT application and high TAPSE at baseline were associated with low Qs_2.

It was found that the PESI score and $TAPSE_2$ negatively affected TAPSE change, while the application of USAT increased TAPSE change. When examining the effect of variables on $TAPSE_2$, a history of atrial fibrillation was associated

Table 3. Post-treatment Clinical, Echocardiographic, and Tomographic Measurements

	USAT n = 203	Anticoagulant n = 222	All Patients n = 425	*P*
SBP, mm Hg	125 ± 13.8	126 ± 17.3	125 ± 15.7	.787
DBP, mm Hg	75.7 ± 9.8	76.3 ± 9.9	76.1 ± 9.8	.678
Hear rate, /min	82.1 ± 10.6	86.2 ± 12	84.2 ± 11.5	<.001
Oxygen saturation, %	94.8 ± 2.6	94 ± 3.2	94.4 ± 3	.032
TAPSE, mm	22.9 ± 4	21.7 ± 3.9	22.3 ± 4	.007
S', cm/s	14.2 ± 2.4	13.6 ± 2.8	14 ± 2.6	.100
PAPs, mm Hg	36.3 ± 9.4	39.3 ± 13.5	37.7 ± 11.6	.016
Qanadli score	9.1 ± 5.2	12.8 ± 6.2	10.6 ± 5.9	<.001
RV/LV_2 ratio	0.91 ± 0.11	0.93 ± 0.14	0.92 ± 0.12	.098
RA/LA_2 ratio	1.13 ± 0.21	1.01 ± 0.17	1.09 ± 0.2	<.001
Main PA diameter, mm	28.1 ± 4.3	28.6 ± 4	28.3 ± 4.2	.378
Left PA diameter, mm	21.2 ± 3.2	22 ± 2.7	21.6 ± 3	.009
Right PA diameter, mm	21.8 ± 3.5	23.2 ± 3.1	22.5 ± 3.4	<.001
Main PA/Aorta ratio	0.84 ± 0.13	0.84 ± 0.13	0.84 ± 0.13	.970
Pleural effusion, n (%)	81 (39.9)	66 (29.7)	147 (34.6)	.074
Pulmonary infarction, n (%)	75 (33.8)	44 (21.6)	119 (28)	.002

LA, left atrium; LV, left ventricle; PA, pulmonary artery; PAPs, pulmonary artery systolic pressure; RA, right atrium; RV, right ventricle; S', right ventricle tissue doppler; TAPSE, tricuspid annular plane systolic excursion. 1, measurement at admission; 2, measurement after treatment.

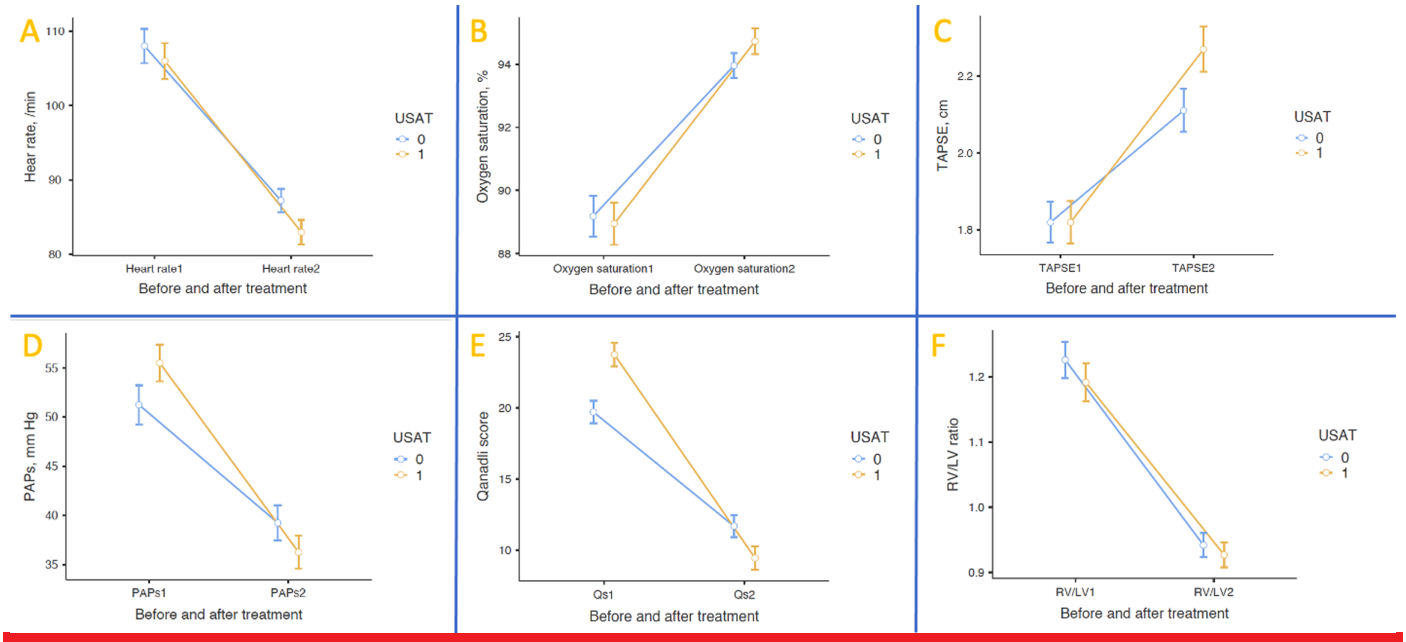

Figure 2. Changes in heart rate (A), oxygen saturation (B), TAPSE (C), PABs (D), Qs (E), and RV-LV ratio (F) before and after treatment in the USAT and anticoagulant groups.

with low $TAPSE_2$, whereas USAT application and high $TAPSE_1$ were associated with high $TAPSE_2$.

From a safety perspective, it was found that the USAT group had a higher incidence of major and minor bleeding compared to the anticoagulant group, but no difference was observed in mortality due to any cause during hospitalization (Supplementary Tables).

DISCUSSION

The study represents the largest single-center data comparing USAT and anticoagulant treatment in patients with acute PE at IHR. In this study, it was demonstrated that USAT is superior to anticoagulant treatment in terms of effectiveness, showing greater reduction in thrombus burden, improvement in RV function, and better clinical parameter outcomes. In the USAT group, the significant reduction in PAP, confirmed by invasive measurements, also supports this result. Although the superiority of USAT in terms of effectiveness has been demonstrated, this increased effectiveness is also associated with a slightly elevated risk of bleeding. This highlights the importance of careful patient selection through the assessment of bleeding risk and comorbidities on a patient-by-patient basis.

Table 4. Changes in Clinical and Imaging Measurements of Patients

	Mean Change (Standard Error)		
	USAT	Anticoagulant	*P*
Heart rate, /min	23 (1.2)	20.8 (1.2)	.007
Oxygen saturation, %	5.8 (0.3)	4.7 (0.3)	.015
TAPSE, cm	0.45 (0.03)	0.29 (0.02)	<.001
Qs	14.3 (0.4)	8 (0.4)	<.001
RV/LV ratio	0.26 (0.01)	0.28 (0.01)	.378
PABs, mm Hg	19.2 (0.9)	12 (1)	<.001

LV, left ventricle; PAPs, pulmonary artery systolic pressure; Qs, Qanadli score; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

The ULTIMA study is the first randomized clinical trial to demonstrate the superior efficacy of USAT over anticoagulation alone.[9] In this study, which included a sample of 59 patients, the primary endpoint was the change in echocardiographic RV/LV ratio at 24 hours after treatment. In this study, which included only intermediate-risk patients with an RV/LV ratio ≥ 1, a greater reduction in the RV/LV ratio was observed in the USAT group compared to anticoagulation (0.30 ± 20 vs. 0.03 ± 16, $P < .001$). Consistent with the RV/LV change, TAPSE change at 24 hours was also significantly more favorable in the USAT group. However, by the 90-day follow-up, the significant changes in RV/LV ratio and RV function observed at 24 hours had converged, resulting in no significant difference between the 2 groups. In terms of safety, no major bleeding was observed in the USAT group, and only minor bleeding occurred in 4 patients. Due to the small sample size, no definitive conclusions about safety can be drawn. Another notable limitation is that follow-up CT was not performed after treatment, so changes in thrombus burden were not assessed. In this study, similar to ULTIMA, a change in RV function favoring USAT was observed, but no significant difference was found in the change of the RV/LV ratio. Some reasons for not observing this difference may include the different risk groups of the patients, the use of CTPA instead of echocardiography for RV/LV ratio assessment in the study, and the fact that follow-up imaging was performed 72-96 hours later in the study.

Another prospective study evaluating the safety and efficacy of USAT is the SEATTLE-II study.[10] This study included

a total of 150 patients from both intermediate and high-risk groups. The primary safety endpoint was major bleeding within 72 hours after the procedure, while the primary efficacy endpoint was the change in RV/LV ratio measured by CTPA at 48 hours. Regarding efficacy endpoints, similar to this study, positive results were observed in RV/LV ratio change, reduction in thrombus burden, and changes in PAP compared to before treatment. Regarding safety, major bleeding occurred in 14 patients (9.3%) within 72 hours, with no instances of intracranial hemorrhage. Although the definitions of major bleeding do not completely overlap with those in the study, both studies observed similar frequencies of major bleeding. In this study, intracranial hemorrhage was found in 4 patients (1.9%), whereas none were observed in the SEATTLE-II study. One reason for this difference could be the variation in bleeding risk profiles and comorbidities of the patients in the study.

Following these studies that demonstrated the efficacy and safety of USAT, another study aimed at determining the optimal tPA dose and infusion duration is the OPTALYSE-PE randomized clinical trial.[11] In this study, 100 patients were randomized into 4 different groups with varying dose regimens. The efficacy endpoints were changes in RV/LV ratio and modified Miller score, while the safety endpoint was major bleeding within 72 hours after the procedure. Although similar results were obtained in terms of RV/LV change between the low-dose and high-dose groups, a significant reduction in thrombus burden was observed with increased dose. Increasing the tPA dose led to a reduction in thrombus burden without a corresponding increase in RV/LV change. It has been suggested that there is no linear relationship or correlation between PA embolic burden and RV dilatation. Additionally, the 1-year long-term follow-up of these patients demonstrated sustained benefits in terms of RV function, functional status, and quality of life.[12] Regarding the safety endpoint, the major bleeding rate, defined similarly to this study, was 4% (including 1% intracranial), while the minor bleeding rate was 7%. Although the rate of major bleeding is similar to the study, the small sample size of the OPTALYSE-PE study and the fact that about one-fifth of the patients were from intermediate-low risk groups, along with stringent exclusion criteria, may mean that the bleeding events do not fully reflect real-world data for USAT treatment. Another limitation of the study is the lack of a control group receiving only anticoagulant therapy.

The KNOCOUT PE registry study is another investigation that addresses the limitations of previous studies, including OPTALYSE-PE, by examining safety endpoints and different dosing strategies with a larger patient cohort.[13] This multicenter registry study, which included a total of 489 patients from only high and intermediate-to-high risk groups, has the primary efficacy endpoint as the change in RV/LV ratio, and the safety endpoint as the frequency of bleeding events defined similarly to the study. The mean tPA dose for all patients was reported as 18.1 ± 7.4 mg, and the mean infusion duration was 10.5 ± 5.37 hours, indicating that a lower dose and shorter duration of treatment were used compared to the study. However, the echocardiographic LV/RV ratio change was found to be 22.6%. The frequency of bleeding events was lower compared to previous studies, with major bleeding reported at 1.6% and intracranial bleeding at 0.9%. Another study comparing conventional CDT to anticoagulation in patients with intermediate-to-high risk acute PE is the CANARY randomized clinical trial.[14] Due to a reduction in patient enrollment caused by disruptions during the COVID-19 pandemic, this study, which had lower statistical power, had a primary endpoint of the percentage of patients with an RV/LV ratio > 0.9 at 3 months of follow-up, and the safety endpoint was bleeding events. Due to the early termination of the study, no significant results were obtained for the primary endpoint. Regarding bleeding events, the CDT group of 46 patients experienced 1 major bleeding event and 3 minor bleeding events.

Although different dosing and infusion duration strategies have been used in USAT studies in the literature, lower doses and infusion durations have been preferred in these studies compared to the single-center results. However, in the single-center series of 225 patients, which includes all risk groups, it has been shown that bleeding events and mortality were not associated with increased tPA dose and infusion duration.[15] Additionally, a linear relationship has been shown between increasing tPA doses and reduction in thrombus burden. In a meta-analysis by Kaymaz et al[16] that evaluated results from 15 studies, the all-cause and cardiovascular mortality rates were reported as 3.2% and 2.2%, respectively, while the rates of major and minor bleeding were reported as 5.5% and 6.9%. To compare with STT, a meta-analysis comparing STT with anticoagulation reported a major bleeding rate of 9.2% in the STT group, whereas the study reported a rate of 5.9%.[17]

Study Limitations

Regarding the limitations of this study, although balance among variables was achieved using PSA methods, the study remains susceptible to bias due to operator-based treatment selection and its observational nature, making it less robust than results from a randomized controlled trial. Although a partially sufficient number of patients (n = 203) was reached for analysis in the treatment group, expanding the control group would lead to more accurate results from PSA methods. While the duration and dose of tPA administration vary from patient to patient in the USAT group, using a single treatment regimen could provide more definitive comparative results. One of the limitations of this study is that the treatment option in the group receiving only anticoagulant therapy was restricted to intravenous heparin, which prevented the comparison of different treatment modalities.

Another limitation is that follow-up CT was performed between 72 and 96 hours, leading to variations in timing between patients. Reviewing the literature, it is noteworthy that as the duration of follow-up imaging for evaluating the RV/LV ratio after treatment increases, the RV/LV ratios between the treatment and control groups tend to converge. This situation could impact one of the efficacy endpoints, specifically the RV/LV ratio and its changes.

Furthermore, longer follow-up data could yield significant results concerning changes in the RV/LV ratio. The results of ongoing randomized clinical trials comparing USAT with anticoagulant therapy in acute PE patients[17-19] will provide stronger evidence regarding efficacy and safety endpoints. Moreover, the lack of triple comparions among USAT, STT with a low-dose/slow-infusion tPA regimen, and anticoagulation-alone cohorts may be considered an important limitation for the optimization of treatments for acute PE at IHR. Finally, the implementation of novel indicators for treatment failure and/or deterioration to normotensive shock or catastrophic PE might reveal more comprehensive data in the evaluation of effectiveness and safety outcomes in these settings.

CONCLUSION

The quasi-experimental study based on real-world data has demonstrated that USAT with a moderate-dose, slow-infusion tPA regimen is superior to anticoagulant therapy alone in patients with acute PE at IHR, in terms of reduction in PA thrombus burden, improvement in RV dysfunction, and better clinical outcomes. However, it was associated with a slight increase in bleeding events. With insights from prospective studies on USAT treatment, evaluating bleeding risk on an individual basis and considering PE progression may justify personalizing tPA doses and infusion durations beyond standard protocols. This personalized approach could position USAT as a first-line treatment for IHR acute PE.

Ethics Committee Approval: The ethical approval for the study was obtained from the Ethics Committee of S.B.Ü. Koşuyolu High Specialization Training and Research Hospital on May 02, 2023, with decision number 2023/07/687.

Informed Consent: Individual patient consent was waived due to the retrospective nature of the study.

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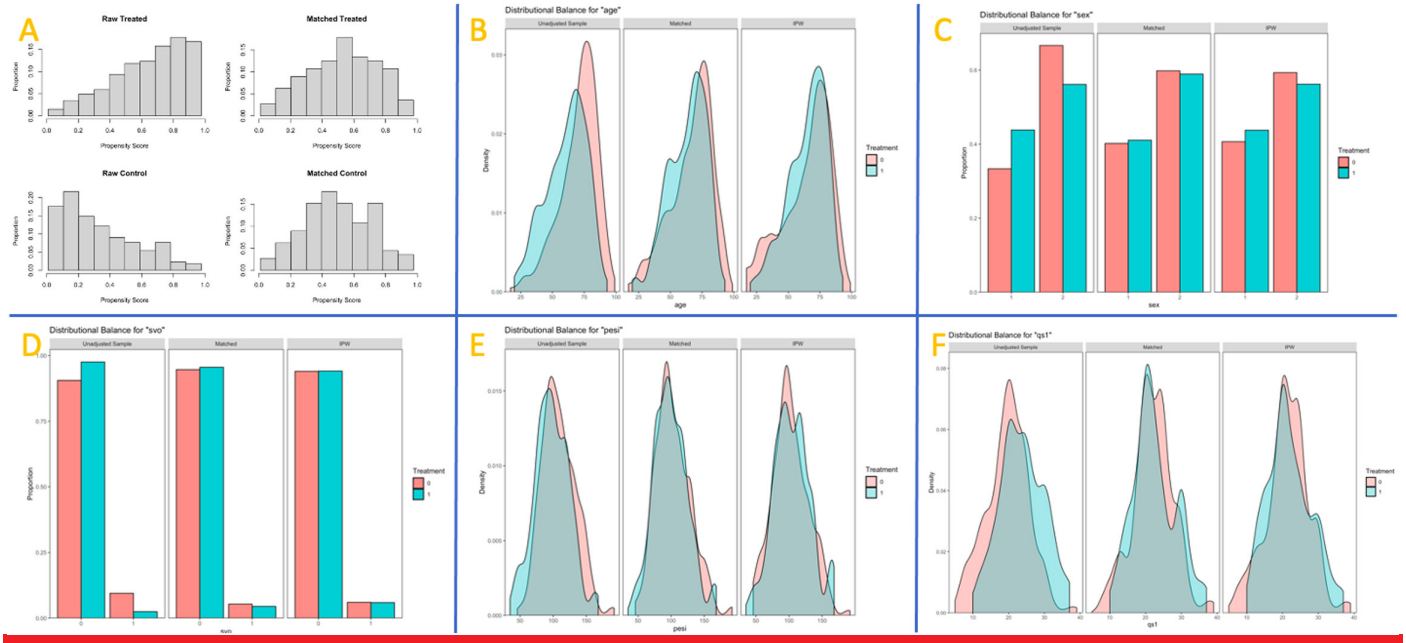

Supplementary Figure 1. Comparison of the treatment and control groups after matching (a) and balancing of the age (b), sex (c), malignancy (d), stroke (e), PESI (f), and Qs_1 (g) variables between groups using PSM and IPW methods.

Supplementary Table 1. Procedural characteristics of USAT

	USAT n = 205		
Bilateral, n (%)	170 (82.9%)		
tPA dose, mg			
Unilateral	27.4 ± 14.5		
Bilateral	38.5 ± 13.6		
Infusion duration, hours	25.2 ± 6.6		
Pulmonary pressures before USAT		Pulmonary pressures after USAT	
PAPs, mm Hg	56.2 ± 15.1	PAPs, mm Hg	40.2 ± 12.6
PAPd, mm Hg	17.5 ± 7.2	PAPd, mm Hg	12.7 ± 5.6
PAPm, mm Hg	30.9 ± 8.5	PAPm, mm Hg	22.6 ± 7.5

Abbreviations: tPA: Tissue plasminogen activator, PAPs: Pulmonary artery systolic pressure PAPd: Pulmonary artery diastolic pressure, PABm: Pulmonary artery mean pressure

Supplementary Table 2. Comparison of bleeding events and in-hospital mortality

	USAT n = 203	Anticoagulant n = 222	All patients n = 425	*P*
Major bleeding, n (%)	12 (5.9%)	2 (0.9%)	14 (3.3%)	0.002
Minor bleeding, n (%)	19 (9.4%)	3 (1.4%)	22 (5.2%)	<0.001
Mortality, n (%)	9 (4.4%)	15 (6.8%)	24 (5.6%)	0.300

Supplementary Table 3. Bleeding events in the USAT group

Event	Number of patients
In-hospital mortality	**9**
Intracranial bleeding	3
Major non-intracranial bleeding	1
Unresolving PE	5
Major bleeding	**12**
Intracranial bleeding	4
Hemoptysis	4
Groin hematoma	2
Gastrointestinal bleeding	2
Minor bleeding	**19**
Hemoptysis	4
Groin hematoma	7
Gastrointestinal bleeding	1
Hematuria	1
Other (oral bleeding, bleeding at peripheral vascular access sites etc.)	6

Supplementary Table 4. Multiple linear regression for RV/LV_2 change

Variable	Coefficient	Standard error	Confidence interval (95%)	*P*
RV/LV_1	0.854	0.062	0.763; 0.944	<0.001
PESI	−0.001	0.0005	−0.002; −0.0006	0.001
Qs_1	0.0002	0.001	−0.002; 0.003	0.845
USAT	−0.009	0.018	−0.045; 0.025	0.587
Hear rate	0.0005	0.0004	−0.0003; 0.001	0.23
Syncope	0.035	0.021	−0.007; 0.078	0.103
CAD	−0.009	0.027	−0.063; 0.043	0.715
HF	−0.011	0.054	−0.118; 0.094	0.828

Supplementary Table 5. Multiple linear regression for RV/LV_2

Variable	Coefficient	Standard error	Confidence interval (95%)	*P*
RV/LV_1	0.132	0.04	0.053; 0.211	0.001
PESI	0.001	0.0006	−0.0002; 0.0023	0.123
Age	0.0008	0.0006	−0.0003; 0.002	0.173
Gender	0.015	0.019	−0.022; 0.054	0.42
USAT	0.009	0.017	−0.025; 0.043	0.591
Oxygen saturation	0.001	0.002	−0.002; 0.004	0.599
AF	0.084	0.046	−0.006; 0.176	0.068
CAD	0.009	0.024	−0.039; 0.058	0.695
COPD	0.03	0.026	−0.021; 0.083	0.249

Supplementary Table 6. Multiple linear regression for Qs_2 change

Variable	Coefficient	Standard error	Confidence interval (95%)	*P*
RV/LV_1	−2.538	1.623	−5.73; 0.65	0.118
PESI	−0.018	0.015	−0.048; 0.012	0.241
Qs_1	0.424	0.058	0.31; 0.54	<0.001
USAT	3.75	0.64	2.48; 5.01	<0.001
Age	0.01	0.03	−0.05; 0.07	0.688
Gender	−0.378	0.7	−1.76; 1.01	0.589
Syncope	1.25	0.79	−0.3; 2.81	0.114
SBP	−0.016	0.015	−0.046; 0.014	0.293
HF	−3.198	1.47	−6.09; −0.307	0.03
Malignancy	−0.45	0.85	−2.12; 1.21	0.593

Supplementary Table 7. Multiple linear regression for Qs_2

Variable	Coefficient	Standard error	Confidence interval (95%)	*P*
RV/LV_1	1.561	1.571	−1.527; 4.649	0.321
PESI	−0.0001	0.014	−0.029; 0.029	0.989
Qs_1	0.512	0.059	0.394; 0.629	<0.001
USAT	−3.689	0.625	−4.918; −2.459	<0.001
Hear rate	0.004	0.02	−0.035; 0.044	0.821
Oxygen saturation	−0.089	0.07	−0.228; 0.049	0.206
TAPSE	−1.883	0.77	−3.399; −0.368	0.015

Supplementary Table 8. Multiple linear regression for TAPSE

Variable	Coefficient	Standard error	Confidence interval (95)%	*P*
RV/LV_1	−0.077	0.092	−0.259; 0.103	0.398
PESI	−0.004	0.001	−0.006; −0.002	<0.001
Qs_1	0.0009	0.003	−0.005; 0.007	0.778
USAT	0.084	0.04	0.003; 0.165	0.04
Syncope	0.108	0.06	−0.022; 0.239	0.103
Oxygen saturation	−0.007	0.004	−0.016; 0.02	0.139
$TAPSE_1$	−0.54	0.053	−0.64; −0.43	<0.001

Supplementary Table 9. Multiple linear regression for $TAPSE_2$

Variable	Coefficient	Standard error	Confidence interval (95%)	*P*
RV/LV_1	−0.085	0.083	−0.25; 0.078	0.304
PESI	−0.002	0.001	−0.004; 0.001	0.077
Age	−0.002	0.002	−0.006; 0.002	0.329
Gender	−0.005	0.046	−0.097; 0.087	0.913
USAT	0.092	0.039	0.015; 0.17	0.019
Heart rate	−0.001	0.001	−0.003; 0.001	0.418
Oxygen saturation	−0.005	0.004	−0.015; 0.003	0.220
SBP	0.001	0.001	−0.001; 0.003	0.402
$TAPSE_1$	0.405	0.054	0.298; 0.513	<0.001
HF	−0.085	0.119	−0.321; 0.15	0.477
CAD	−0.101	0.054	−0.208; 0.004	0.060
AF	−0.263	0.095	−0.45; 0.075	<0.001