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Effectiveness and Safety of Reduced-Dose and Slow-Infusion Intravenous Tissue-Type Plasminogen Activator Regimen in Patients with Acute Pulmonary Embolism at Intermediate-High Risk

ORIGINAL INVESTIGATION

Barkın Kültürsay[1]
Seda Tanyeri[2]
Berhan Keskin[3]
Hacer Ceren Tokgöz[2]
Dicle Sırma[2]
Çağdaş Buluş[2]
Şeyma Zeynep Atıcı[2]
Şeyma Nur Çiçek[2]
Furkan Baturalp Erdoğan[2]
Ahmet Sekban[2]
Mustafa Bulut[4]
Zübeyde Bayram[2]
Selahattin Akyol[2]
Aykun Hakgör[3]
Şeyhmus Külahçıoğlu[2]
Ali Karagöz[2]
Nihal Özdemir[2]
Cihangir Kaymaz[2]

[1]*Department of Cardiology, Tunceli State Hospital, Tunceli, Türkiye*
[2]*Department of Cardiology, University of Health Sciences, Koşuyolu Heart Training and Research Hospital, İstanbul, Türkiye*
[3]*Department of Cardiology, Medipol University Faculty of Medicine, İstanbul, Türkiye*
[4]*Department of Cardiology, Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital, Trabzon, Türkiye*

Corresponding author:
Cihangir Kaymaz
✉ cihangirkaymaz2002@yahoo.com

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ABSTRACT

Background: Intermediate-high-risk (IHR) pulmonary embolism (PE) is defined by right ventricular (RV) dysfunction and elevated cardiac troponin in the absence of hemodynamic instability. While full-dose thrombolysis may improve outcomes, it poses a high bleeding risk. This study assessed the safety and efficacy of a reduced-dose, slow-infusion thrombolytic regimen.

Methods: This single-center retrospective study included 124 patients with acute IHR PE who met at least one of the following criteria: systolic blood pressure ≤110 mm Hg, heart rate >100 bpm, SpO_2 <90% on room air, respiratory rate >20/min, or lactate >2 mmol/L. Patients with contraindications to thrombolysis or symptom onset >14 days were excluded. Patients received 25 mg intravenous alteplase (t-PA) infused over 4-6 hours, along with standard anticoagulation according to the institutional protocol. Following the initial dose, a repeat infusion of 25 mg over 4-6 hours was administered if tachycardia, hypoxia, or signs of organ hypoperfusion persisted on re-evaluation.

Results: Syncope was the presenting symptom in 27.4%, and 49.2% had deep vein thrombosis. Median t-PA dose was 50 mg and median infusion duration was 6 hours. Significant improvements were observed in RV and RA size/function, thrombus burden, and clinical parameters (all $P < .001$). Qanadli score and RV/LV ratio decreased by 55% and 29%, respectively. Major and minor bleeding occurred in 4.8% and 3.2%. In-hospital mortality was 4.8%; 12-month survival was 89.5%. Chronic thromboembolic pulmonary hypertension developed in 3.2%.

Conclusion: Low-dose, slow-infusion t-PA therapy appears effective and well-tolerated, offering hemodynamic and clinical benefit with fewer bleeding complications in patients with IHR PE.

Keywords: Alteplase, pulmonary embolism, thrombolysis

INTRODUCTION

High-risk (HR) pulmonary embolism (PE), a lethal condition, presents with hemodynamic instability and requires urgent reperfusion treatment. Intermediate-high-risk (IHR) PE, on the other hand, presents with right ventricular (RV) dysfunction and elevated circulating cardiac troponin levels, even when the patient appears hemodynamically stable at the time of presentation. However, there is a residual risk of deterioration toward hemodynamic instability in patients at IHR status. Although full-dose systemic thrombolytic treatment (STT) is effective in reducing all-cause mortality and preventing hemodynamic collapse in these patients, this treatment is also associated with increased risks of intracranial or other life-threatening bleeding, which has previously been confirmed in 2 meta-analyses.[1-3] Therefore, current guidelines do not recommend STT as the first-line treatment strategy for IHR PE.[4]

Considering the balance between benefits and risks, reduced-dose STT regimens are gaining popularity in clinical practice globally. This study aimed to evaluate

the safety of a reduced-dose STT regimen while maintaining effective reperfusion in patients with acute IHR PE.

METHODS

Design

Between 2012 and April 2025, a total of 976 patients with acute PE were admitted to the center. The systematic work-up for the diagnosis of acute PE, and initial risk stratification comprising the multidetector contrast-enhanced computed tomography (CT) angiography and transthoracic echocardiography (TTE) assessments, PE severity indexes, and biomarker evaluation has been based on the criteria recommended by the European Society of Cardiology/European Respiratory Society 2019 PE guidelines.[3] Among these, patients identified as IHR were screened, and 124 patients who met the inclusion criteria were ultimately included in the study (Figure 1).

The inclusion criteria were at least one of the following: systolic blood pressure ≤ 110 mm Hg, heart rate > 100 bpm, pulse oximetric saturation (SpO_2) < 90% on room air, respiratory rate >20 breaths per minute, or serum lactate >2 mmol/L. Exclusion criteria were the presence of any contraindication for STT, age < 18 years, and duration from symptom onset to PE diagnosis >14 days. The thrombolytic treatment strategy was implemented as part of an institutional protocol. According to the institutional protocol, patients who met the inclusion criteria and none of the exclusion criteria received initial weight-adjusted UFH, followed by a 25 mg intravenous infusion of tissue-type plasminogen activator (t-PA, alteplase) over 4-6 hours. After this first infusion, a bedside clinical reassessment was performed. If any of the following criteria were still present—heart rate > 100 bpm, SpO_2 < 90%, or signs of organ hypoperfusion—a second 25 mg t-PA infusion was administered in the same manner. In the case of persistent clinical deterioration, repeated infusions were given according to the same dosing strategy.

HIGHLIGHTS

- This study evaluates a low-dose, slow-infusion alteplase protocol in intermediate-high risk pulmonary embolism (PE) patients. The median t-PA dose was 50 mg and median infusion duration was 6 hours.
- Most patients required more than 1 infusion of 25 mg alteplase for adequate response.
- Treatment led to significant improvements in hemodynamic parameters, including heart rate, oxygen saturation, pulmonary artery systolic pressure, right ventricular/left ventricular ratio, and Qanadli score.
- Major bleeding occurred in only 4.8% of patients; intracranial hemorrhage occurred in 0.8%.
- In-hospital mortality was 4.8%; 12-month survival was 89.5%. Chronic thromboembolic pulmonary hypertension developed in 3.2%.
- These findings support that low-dose slow-infusion thrombolysis is a safe and effective alternative in managing IHR PE.

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[5] [Qanadli score (QS)], 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. The 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 systolic pressures (PASP) were calculated from the tricuspid regurgitation jet. All measurements and assessments were made in accordance with the American Society of Echocardiography guidelines.[6]

The data were collected retrospectively from hospital records. Given the retrospective design and inclusion of the entire eligible patient cohort, power analysis was not performed. Follow-up data were obtained through review of electronic medical records and hospital databases. The study protocol was approved by the Institutional Ethics Committee (Approval No: 2025/06/1093, Approval Date: April 22, 2025), and all procedures were conducted in accordance with the Declaration of Helsinki.

Clinical effectiveness outcomes were all-cause mortality in 30 days, resolution of thrombus on CT as assessed by QS, and reduction in right ventricle to left ventricle diameter ratio (RV/LVr) on CT. For safety outcomes, major bleeding was defined as overt bleeding associated with a fall in the hemoglobin level of at least 2 g/dL, or with transfusion of 2 units of packed red blood cells, or involvement of a critical site.[7] Clinically overt bleeding not fulfilling the criteria for major bleeding was classified as a minor bleeding complication.

Statistical Analysis

All statistical analyses were performed using R version 4.3.1 (R Project, Vienna, Austria) and Jamovi Version 2.6.19.0. 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. Normality of the data was determined using histograms and the Shapiro–Wilk test. The paired sample *t*-test and Wilcoxon signed-rank test were used for pre- and post-treatment comparisons, as appropriate. Single-arm Kaplan–Meier survival analysis was performed, and censoring was applied for individuals without events at the end of the follow-up period. A *P* value of <.05 was considered the limit for statistical significance. During the preparation of this article, the authors did not use artificial intelligence-assisted technologies.

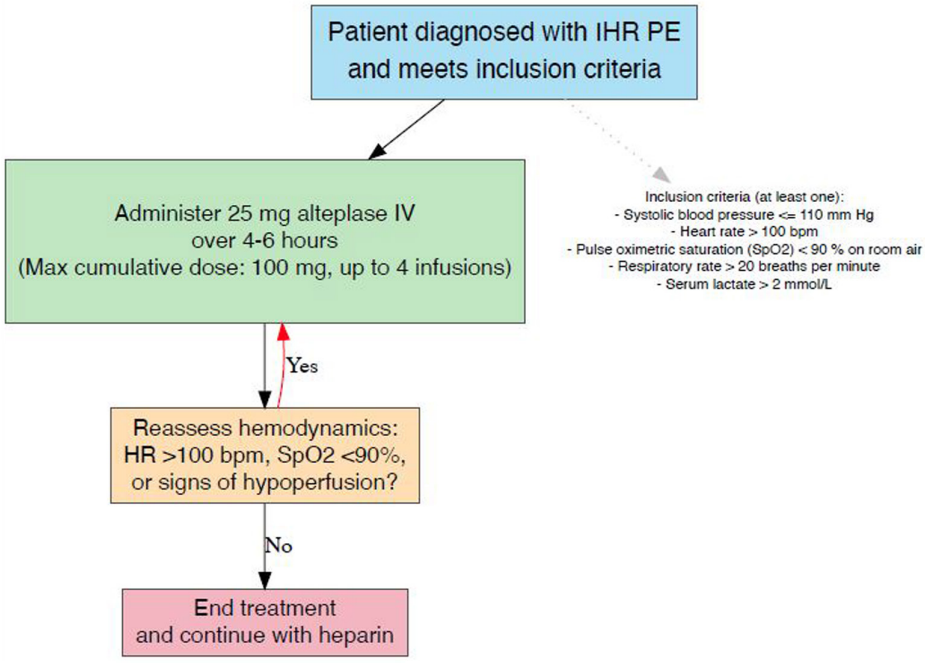

Figure 1. Treatment algorithm for reduced-dose, slow-infusion systemic thrombolysis in patients with intermediate-to-high-risk pulmonary embolism (IHR PE). Patients diagnosed with IHR PE and meeting at least one of the predefined inclusion criteria (systolic blood pressure ≤110 mmHg, heart rate >100 bpm, pulse oximetric saturation <90% on room air, respiratory rate >20 breaths/min, or serum lactate >2 mmol/L) received an initial 25 mg intravenous infusion of alteplase over 4–6 hours. Following each infusion, bedside hemodynamic reassessment was performed, including evaluation of heart rate, oxygen saturation, and signs of hypoperfusion. In cases of persistent hemodynamic compromise, additional 25 mg alteplase infusions were administered according to the same protocol, with a maximum cumulative dose of 100 mg (up to 4 infusions). If clinical stability was achieved, thrombolysis was discontinued, and anticoagulation with unfractionated heparin was continued as per standard care.

RESULTS

Baseline Characteristics

Patient characteristics are summarized in Table 1. The mean age of patients with acute PE at IHR status was 55 ± 15.8 years, and 58.9% were female. The median duration from the onset of symptoms consistent with acute PE to confirmed diagnosis was 3 (2-7) days, and 27.4% presented with syncope. Regarding comorbidities, hypertension, diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease were documented in 19.3%, 10.5%, 1.6%, and 3.2% of patients, respectively. A history of PE and deep vein thrombosis was noted in 12.1% and 49.2% of patients. Potential predisposing or prothrombotic factors for acute PE included malignancy in 4.8% of patients, recent orthopedic surgery or fractures in 4.8%, postoperative status in 15.3%, long-haul travel by air or car in 3.2%, and immobility in 8.1%. The mean pulmonary embolism severity index (PESI) score was 95.5 ± 29.2, with a median PESI class of 3 (2-4), Simplified PESI score of 1 (1-2), and a mean modified shock index of 1.02 ± 0.26.[8]

Prior to treatment, the mean heart rate was 112 ± 16.6 beats per minute, systolic blood pressure was 123 ± 14.9 mm Hg, and SpO_2 was 89% (85%-93%). Laboratory analysis revealed median serum lactate levels of 2.35 mmol/L (1.6-2.9), troponin levels of 0.096 ng/mL (0.04-0.27), D-dimer levels of 9.82 U/mL (5.13-18.5), and C-reactive protein levels of 23.1 mg/L (11.6-45.3).

Clinical and Hemodynamic Outcomes

Mean and median doses of t-PA were 47.5 ± 24.1 and 50 (range: 25-50) mg, respectively. Mean and median duration of low-dose t-PA infusions were 7.44 ± 5.31 and 6 (range: 4-10) hours, respectively. Second, third, and fourth t-PA infusions were required in 73 patients (58.9%), 24 patients (19.3%), and 14 patients (11.3%), respectively. The administered overall t-PA doses were 25 mg in 51 patients (41.1%), 50 mg in 49 patients (39.5%), 75 mg in 10 patients (8.0%), and 100 mg in 14 patients (11.3%) (Table 2) (Figure 2).

Following the low-dose tPA infusion(s), significant improvements were observed in clinical and hemodynamic status, PA thrombotic obstruction, and RV function (Table 3) (Figure 3). Decrease in the heart rate from 112 ± 18.6 bpm to 82.2 ± 11.3 bpm ($\Delta = -29.7$ bpm, $P < .001$) and increase in the pulse SpO_2% from 89 (85-93) to 96 (94-97.3) ($\Delta = 6.5$, $P < .001$) were consistent with overall circulatory stabilization. Pulmonary artery systolic pressure decreased from 50.9 ± 13.3 mm Hg to 34.4 ± 12.6 mm Hg ($\Delta = -17.7$ mm Hg, $P < .001$), accompanied by a significant reduction in the QS from 20 (18-23) to 9 (6.75-13) ($\Delta = -10$, $P < .001$). Similarly, the RV/LVr improved from 1.26 ± 0.21 to 0.89 ± 0.13 ($\Delta = -0.37$, $P < .001$), reflecting a reversal of RV dilation due to pressure strain. These changes were accompanied by decreases in the main pulmonary artery diameter from 30.4 mm (28-32) to 28 mm (25.3-30) ($\Delta = -2.31$ mm, $P < .001$) and right atrial to left atrial diameter ratio (RA/LAr) from 1.31 ± 0.26 to 1.02 ± 0.18 ($\Delta = -0.30$, $P < .001$), and

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	All, n = 124
Age (years)	55 ± 15.8
Male sex, n (%)	51 (41.1)
Diabetes mellitus, n (%)	13 (10.5)
Hypertension, n (%)	24 (19.3)
Atrial fibrillation, n (%)	2 (1.6)
Syncope	34 (27.4)
Chronic obstructive lung disease, n (%)	4 (3.2)
Previous coronary artery disease, n (%)	7 (5.6)
Previous pulmonary embolism, n (%)	15 (12.1)
Presence of deep vein thrombosis, n (%)	61 (49.2)
Possible secondary causes, n (%)	
Malignancy	6 (4.8)
Orthopedic surgery/fractures	6 (4.8)
Prolonged traveling	4 (3.2)
Postoperative status	19 (15.3)
Immobility	10 (8.1)
Baseline vital signs	
Heart rate/min	112 ± 16.6
Systolic blood pressure, mm Hg	127 ± 21.9
Diastolic blood pressure, mm Hg	79 ± 18.6
Oxygen saturation, %	89 (85-93)
Baseline laboratory variables	
Troponin, ng/mL	0.096 (0.04-0.27)
Lactate, mmol/L	2.35 (1.6-2.9)
D-dimer, U/mL	9.82 (5.13-18.5)
C-reactive protein	23.1 (11.6-45.3)
Symptom duration (days)	3 (2-7)
PESI	95.5 ± 29.2
PESI class	3 (2-4)
Simplified PESI	1 (1-2)
Modified shock index	1.02 ± 0.26
Pulmonary infarction, n (%)	16 (12.9)
Pleural effusion, n (%)	12 (9.7)

PESI, pulmonary embolism severity index.

improved RV free-wall longitudinal systolic function, as evidenced by an increase in TAPSE from 1.81 ± 0.39 cm to 2.3 ± 0.3 cm (Δ = +0.46 cm, $P < .001$).

Primary Clinical Outcomes and Bleeding Complications

The observed in-hospital mortality rate was 4.8%, with 2 fatalities (1.6%) attributed to major bleeding and 4 (3.2%) due to hemodynamic decompensation. Importantly, no cases of recurrent PE or hemodynamic deterioration were recorded during the 30-day follow-up period. Notably, only 1 patient (0.8%) experienced intracranial (cerebellar) hemorrhage, which did not require surgical intervention, and the patient was discharged without neurological sequelae. Among the 6 major bleedings, 1 occurred after 100 mg t-PA infusion, 4 after 50 mg, and 1 after 25 mg.

Table 2. Thrombolytic Dosing Regimens and Safety Outcomes

	All, n = 124
tPA dose, mg	50 (25-50)
tPA infusion duration, hours	6 (4-10)
tPA infusion rate, mg/hours	6 (4-10)
Requirement following the first infusion	
Second infusion (50 mg)	73 (58.9%)
Third infusion (75 mg)	24 (19.3%)
Fourth infusion (100 mg)	14 (11.3%)
tPA dose groups	
25 mg	51 (41.1%)
50 mg	49 (39.5%)
75 mg	10 (8%)
100 mg	14 (11.3%)
Major bleeding, n (%)	6 (4.8)
Minor bleeding, n (%)	4 (3.2)
In hospital mortality	6 (4.8%)

Median follow-up duration was 3045 (2563-3096) days, and the estimated 12-month overall survival rate was 89.52% (95% CI: 84.28%-95.07%) (Figure 4). No patients were lost to follow-up within the first 12 months. During the follow-up period, chronic thromboembolic pulmonary hypertension (CTEPH) developed in 4 patients (3.2%).

DISCUSSION

This study provides compelling evidence that a low-dose, slow-infusion tPA regimen offers a favorable alternative in the management of IHR PE, while maintaining the clinical and hemodynamic benefits of full-dose STT and mitigating bleeding risks.

The fundamental goal of thrombolysis in PE is rapid pulmonary reperfusion and RV unloading, preventing hemodynamic deterioration and RV failure. However, the management of IHR PE presents a significant therapeutic challenge, balancing the need for effective reperfusion therapy against the risk of major bleeding complications. While STT remains a recommended option in select cases, concerns over hemorrhagic events have driven the exploration of alternative dosing strategies.

In this study, the inclusion criteria were designed to better define the upper zone of IHR PE patients, adopting parameters from the PEITHO trial's subgroup analysis. This approach aimed to capture patients with subtle yet clinically meaningful hemodynamic compromise, who may benefit from early reperfusion therapy but are at elevated bleeding risk with full-dose STT.[1]

The median administered t-PA dose was 50 mg (range: 25-50 mg), with a mean of 47.5 ± 24.1 mg. The median infusion duration was 6 hours (range: 4-10 hours), and the mean was 7.4 ± 5.3 hours. Multiple infusions were needed: 58.9% had a second dose, 19.3% a third, and 11.3% a fourth. Doses of 25 mg and 50 mg were used in 41.1% and 39.5% of patients, respectively. The rest required cumulative doses of 75 mg or more. The study's mortality rate was lower than that reported

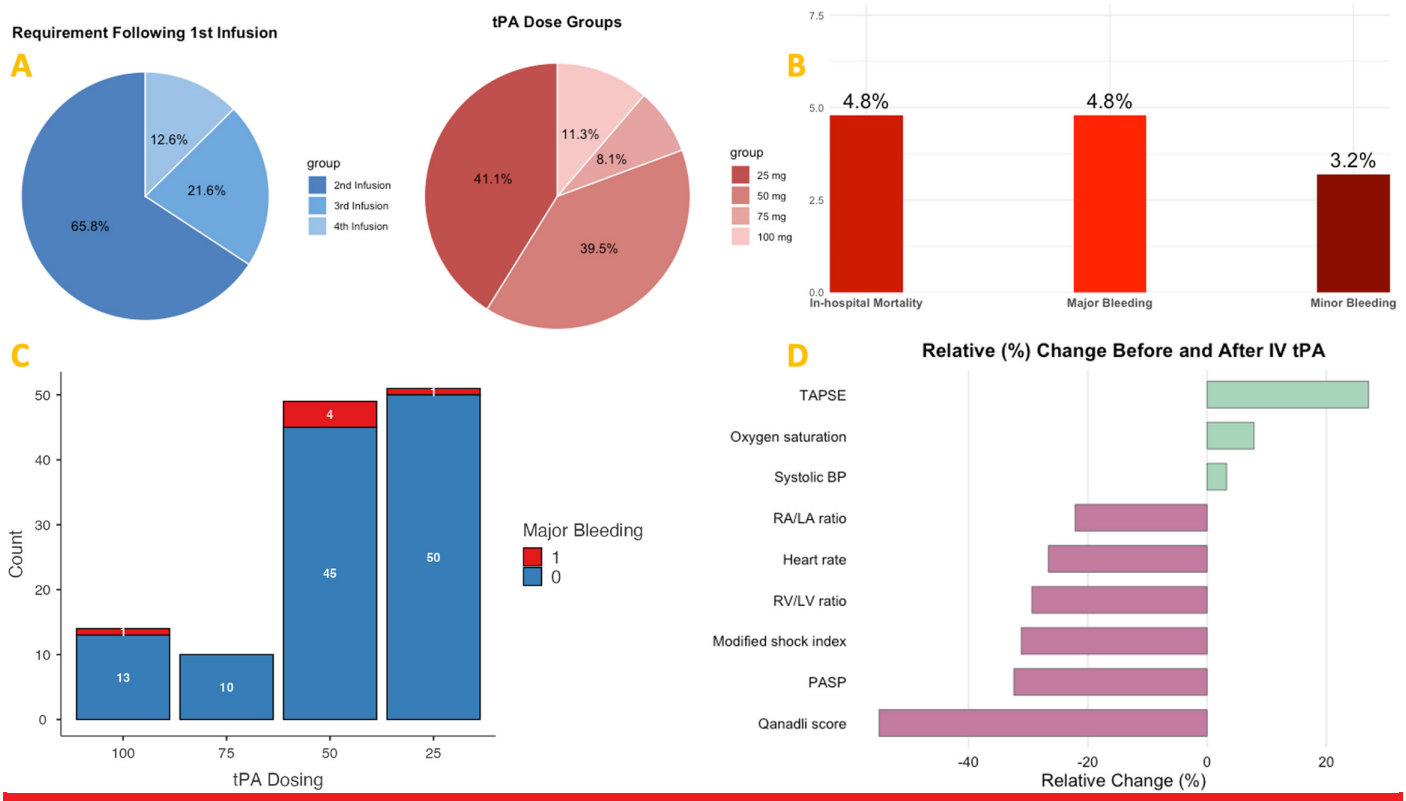

Figure 2. A. Two pie charts depicting infusion data. The first pie chart shows the percentage of patients requiring second, third, and fourth t-PA infusions following the initial dose. The second pie chart illustrates the distribution of patients across different t-PA dose groups. B. Bar plot illustrating the percentages of in-hospital mortality, major bleeding, and minor bleeding events among patients. C. Bar plot comparing the incidence of major bleeding events across different t-PA dose groups. D. Changes in clinical, echocardiographic, and tomographic parameters before and after t-PA infusion.

in the fibrinolytic arm of the PEITHO trial, suggesting that low-dose tPA may reduce risk effectively with better safety. Major and minor bleeding rates were 4.8% and 3.2%, respectively, much lower than the 9%-20% major bleeding rates reported in full-dose, short-infusion STT studies.[1-3] In the PEITHO trial, the major bleeding rate in the STT arm was 11.5%, including a 2% incidence of intracranial hemorrhage.

Compared to both STT and ultrasound-assisted catheter-directed thrombolysis (USAT), the cohort's mortality was similar to previous reports, but major and minor bleeding rates were lower than 5.5% and 6.9%, respectively.[9] Compared to those who underwent AngioJet rheolytic thrombectomy, the low-dose, slow-infusion t-PA regimen was associated with lower mortality and reduced rates of both major and minor bleeding while maintaining effective reperfusion.[10,11] These findings support the hypothesis that a reduced-dose STT strategy can substantially lower bleeding risk without compromising therapeutic efficacy.

Significant reductions in PASP, RV/LV, and RA/LA ratios and improvements in TAPSE were observed, suggesting that even low-dose t-PA can improve RV function impaired by thrombotic pressure overload. These findings are consistent with prior evidence suggesting that effective pulmonary thrombus resolution can be achieved with lower doses of thrombolytics, thereby challenging the conventional reliance on full-dose STT regimens.[12-17]

Patients with worse baseline hemodynamics showed marked decreases in heart rate and modified shock index soon after low-dose tPA, indicating effective restoration of cardiac function without losing fibrinolytic effect.

Beyond the immediate hemodynamic improvements, one of the most critical long-term concerns in PE survivors is the development of CTEPH. While early and effective thrombus resolution is hypothesized to reduce this risk, long-term data remain inconclusive, and STT offers no benefit over standard anticoagulation in preventing progression to CTEPH, as demonstrated in the PEITHO trial.[1,18] Moreover, a retrospective study evaluating reperfusion therapies—including STT, catheter-directed thrombolysis (CDT), and mechanical thrombectomy—found no statistically significant difference in terms of CTEPH development between patients who underwent reperfusion therapies (8%) and those treated with anticoagulation alone (5%).[19] In contrast, studies have shown that patients with persistent residual PA obstruction after acute PE are at increased risk of developing CTEPH.[19] The role of fibrinolysis in modifying this risk remains uncertain, as interventions such as CDT and surgical pulmonary embolectomy have been associated with significant reductions in PA obstruction, which may influence long-term hemodynamics.[20] Furthermore, elevated fibrinogen and reduced plasminogen levels after pulmonary endarterectomy for CTEPH were associated with persistent pulmonary hypertension and worse long-term survival.[21] In this cohort, CTEPH developed

Table 3. Clinical and Imaging Changes Pre- and Post-Thrombolytic Treatment

Variables	Before IV tPA	After IV tPA	Mean Change (SE)	*P*
PASP (mm Hg)	50.9 ± 13.3	34.4 ± 12.6	17.7 (1.44)	<.001
RV/LV ratio	1.26 ± 0.21	0.89 ± 0.13	0.369 (0.105)	<.001
RA/LA ratio	1.31 ± 0.26	1.02 ± 0.18	0.301 (0.03)	<.001
TAPSE (cm)	1.81 ± 0.39	2.3 ± 0.3	0.46 (0.04)	<.001
S′ (cm/sec)	11.2 ± 2.74	14.1 ± 2.5	3.05 (0.43)	<.001
Qanadli score	20 (18-23)	9 (6.75-13)	10 (0.71)	<.001
Main PA diameter (mm)	30.4 (28-32)	28 (25.3-30)	2.31 (0.31)	<.001
Heart rate (bpm)	112 ± 18.6	82.2 ± 11.3	29.7 (1.76)	<.001
Systolic BP (mm Hg)	123 ± 14.9	127 ± 21.9	5 (1.86)	.015
Oxygen saturation (%)	89 (85-93)	96 (94-97.3)	6.5 (0.9)	<.001
Shock index	0.902 ± 0.22	0.682 ± 0.15	0.183 (0.02)	<.001
Modified shock index	1.02 ± 0.26	0.702 ± 0.13	0.26 (0.03)	<.001

in 3.2% of patients during follow-up, which is consistent with previously reported incidence rates. Therefore, according to the currently available data, the efficacy of reperfusion strategies in improving clot resolution and RV function during the acute phase cannot yet be mechanistically linked to a reduction in long-term CTEPH risk. The hypothesis that more effective thrombus resolution during the acute phase may causally reduce the risk of CTEPH remains biologically plausible but unproven. Future prospective studies specifically designed to assess this causal relationship are essential to determine whether optimizing reperfusion strategies can modify the long-term trajectory of pulmonary vascular disease in PE survivors.

The historical reliance on full-dose STT regimens has been predicated on the assumption that higher doses yield superior clot resolution. However, accumulating evidence, including the study, suggests that this approach may not be universally necessary. Low-dose regimens have been shown in multiple trials to reduce mortality and morbidity, indicating that a one-size-fits-all approach may not suit IHR PE.[15,22,23] The study adds to this view by showing real-world data that lower STT doses achieve similar short-term results with better safety. The ongoing PEITHO-3 trial has been designed to assess the efficacy of a reduced-dose t-PA regimen compared with standard anticoagulant therapy within 30 days of randomization as the primary end-point in patients with IHR

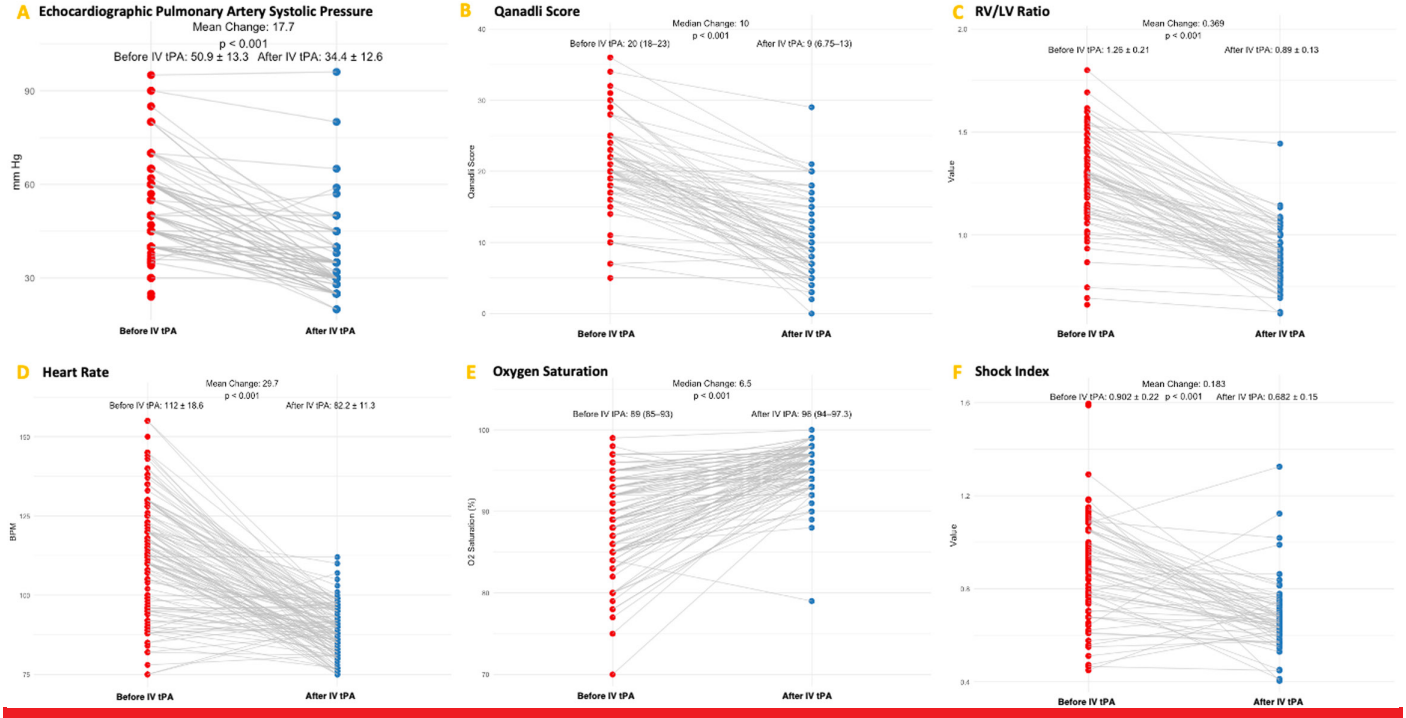

Figure 3. Paired comparison of clinical, echocardiographic, and tomographic parameters before (red dots) and after (blue dots) t-PA infusion. Panels A: Echocardiographic parameters; B and C: Tomographic parameters; D, E, and F: Clinical parameters.

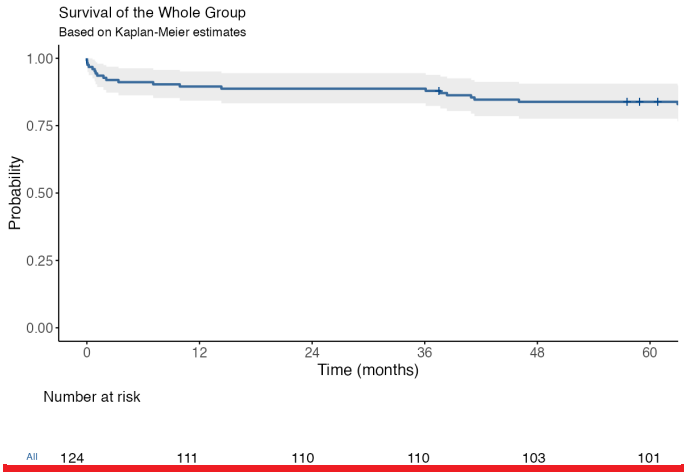

Figure 4. Kaplan-Meier survival plot depicting single-arm survival of the patient cohort.

status. The secondary endpoints include safety, net clinical benefit, impact on overall short-term and long-term mortality, as well as functional impairment, residual RV dysfunction, and incidence of CTEPH.[24] Another important ongoing randomized clinical trial in patients with IHR PE is the HI-PEITHO trial, which compares ultrasound-assisted, low-dose, rapid-infusion thrombolysis with standard anticoagulation. In addition, the STRATIFY trial is currently underway to compare the efficacy and safety of anticoagulation alone, STT, and USAT in this patient population.[25,26] This trial is part of a growing effort to improve the safety profile of reperfusion therapies by using reduced-dose thrombolytics delivered directly to the pulmonary arteries. Prior studies have shown that USAT can effectively reverse RV dysfunction and reduce thrombus burden while significantly lowering the risk of major bleeding events, including intracranial hemorrhage, compared to systemic full-dose thrombolysis.[26-32] Given these favorable safety and efficacy signals, low-dose CDT may represent a promising alternative to STT in selected patients. The results of the HI-PEITHO and STRATIFY trials are expected to clarify whether this approach can be adopted more broadly as a safer reperfusion strategy in IHR PE.[23,24]

Limitations, Clinical Implications, and Future Directions

The findings of this study suggest a rationale for integrating low-dose, slow-infusion STT with t-PA into routine management strategies for IHR PE patients. The balance between hemodynamic efficacy and safety makes it an attractive alternative to both full-dose STT and anticoagulation alone. However, this study has several limitations. First, its retrospective and single-center design may introduce selection bias and limit the generalizability of the findings to broader patient populations and different healthcare settings. Second, the absence of a direct comparator group reduces the ability to draw definitive conclusions regarding the relative effectiveness or superiority of the reduced-dose, slow-infusion regimen.

Future prospective, randomized trials with extended follow-up are essential to determine whether the acute benefits of low-dose thrombolysis translate into durable, long-term advantages, including a potential reduction in CTEPH incidence.[24-26] The causal relationship between more effective thrombus resolution during the acute phase and CTEPH prevention remains speculative and warrants focused investigation. Clarifying this link would have substantial implications for optimizing PE management strategies beyond the immediate treatment period.

Additionally, stratified treatment algorithms—taking into account baseline hemodynamic status, bleeding risk, and RV function—may optimize patient selection, further individualizing management in this setting. The results of the ongoing aforementioned trials are expected to provide answers to these questions.

CONCLUSION

This study provides robust evidence that low-dose, slow-infusion STT with t-PA offers a safe and effective alternative to full-dose STT regimens in IHR PE patients. These findings align with an emerging body of literature suggesting that less-intensive fibrinolytic strategies can maintain efficacy while dramatically improving safety outcomes. With further validation, this approach could transform care for IHR PE.

Ethics Committee Approval: Koşuyolu Heart Training and Research Hospital Ethics Committee approved on April 22, 2025, approval number: 2025/06/1093.

Informed Consent: Due to the retrospective nature of the study, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.K., B.Kültürsay; Design – C.K., H.C.T., A.K.; Supervision – C.K., N.O., Z.B.; Resources – S.K., S.A.; Materials – S.Z.A., C.B., F.B.E.; Data Collection and/or Processing – S.T., B.Keskin., A.H.; Analysis and/or Interpretation – A.H., D.S., A.S.; Literature Search – M.B., S.N.C.; Writing – C.K., B.Kültürsay, H.C.T.; Critical Review – C.K., N.O., H.C.T.

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