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Half-Dose versus Full-Dose Alteplase for Treatment of Pulmonary Embolism

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Abstract

Objectives—Recent evidence suggests that half-dose thrombolysis for pulmonary embolism (PE) may provide similar efficacy with reduced bleeding risk compared to full-dose therapy, but comparative studies are lacking. We aimed to evaluate the effectiveness and safety of half-dose versus full-dose alteplase for treatment of PE.

Design—A retrospective cohort study comparing outcomes in patients receiving half-dose (50 mg) versus full-dose (100 mg) alteplase for PE. We used propensity score matching and sensitivity analyses to address confounding and hospital-level clustering.

Setting—Data from 420 hospitals obtained from the Premier Healthcare Database between January 2010 and December 2014.

Subjects—Adult critically ill patients with acute PE treated with intravenous alteplase therapy.

Interventions—None

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Measurements and Main Results—This study included 3,768 patients: 699 (18.6%) in the half-dose and 3,069 (81.4%) in the full-dose group. At baseline, patients receiving half-dose alteplase required vasopressor therapy (23.3% vs. 39.4%, $p<0.01$) and invasive ventilation (14.3% vs. 28.5%, $p<0.01$) less often, compared to full-dose. After propensity matching ($n=548$ per group), half-dose alteplase was associated with increased treatment escalation (53.8% vs. 41.4%, $p<0.01$), driven mostly by secondary thrombolysis (25.9% vs. 7.3%, $p<0.01$) and catheter thrombus fragmentation (14.2% vs. 3.8%, $p<0.01$). Hospital mortality was similar (13% vs. 15%, $p=0.3$). There was no difference in cerebral hemorrhage (0.5% vs. 0.4%, $p=0.67$), gastrointestinal bleeding (1.6% vs. 1.6%, $p=0.99$), acute blood loss anemia (6.9% vs. 4.6%, $p=0.11$), use of blood products ($p>0.05$ for all), or documented fibrinolytic adverse events (2.6% vs. 2.8%, $p=0.82$).

Conclusions—Compared to full-dose alteplase, half-dose was associated with similar mortality and rates of major bleeding. Treatment escalation occurred more often in half-dose treated patients. These results question whether half-dose alteplase provides similar efficacy with improved safety, and highlights the need for further study before use of half-dose alteplase therapy can be routinely recommended in patients with PE.

Keywords

Thrombolysis; Thrombolytic; Dose; Bleeding; Venous Thromboembolism; Intensive Care Unit

Introduction

Pulmonary embolism is a common disease with approximately 100 cases per 100,000 person years worldwide (1, 2). Mortality in patients hospitalized with acute pulmonary embolism is significant, with a fatality rate of approximately 3–8% in intermediate-risk (submassive), and 25–52% in patients with high-risk (massive) pulmonary embolism (3–5). Patients who survive pulmonary embolism to hospital discharge may develop chronic thromboembolic pulmonary hypertension and reduced functional capacity (6–8).

Thrombolytic therapy is an established treatment option for patients with high-risk pulmonary embolism (9, 10). However, the use of thrombolytic therapy in patients with intermediate risk pulmonary embolism is controversial due to less clear delineation between benefits and risks (3, 10–14). The majority of evidence supporting use of thrombolytic therapy for intermediate risk pulmonary embolism focuses on minimizing treatment escalation, and expediting return to normal functional status with reduced risk of pulmonary hypertension, rather than demonstrating reduced mortality (3, 6, 11, 12). These less definitive clinical benefits of thrombolytic therapy in this setting are tempered by the risk of cerebral hemorrhage and major bleeding, which may be as high as 2% and 6%, respectively (11). Given the potential for bleeding and the premise that the pulmonary vasculature receives the majority of any intravenously administered thrombolytic dose, it has been suggested that lower dose thrombolytics may provide sufficient efficacy, while reducing the risk of major bleeding (6, 15–18). This hypothesis is supported by recent evidence suggesting that using half the usual dose of alteplase in the setting of pulmonary embolism may be effective with a reduced bleeding risk (6, 16, 17). However, there is currently limited evidence comparing treatment outcomes between full-dose and lower dose thrombolytic strategies for managing patients with acute pulmonary embolism.

We conducted a multicenter pharmacoepidemiologic study to compare the effectiveness of half-dose versus full-dose alteplase for the treatment of patients with acute pulmonary embolism admitted to the intensive care unit (ICU). Our primary outcome was to assess the need for treatment escalation between groups. Additionally, we aimed to determine differences in safety, important clinical outcomes, and cost. We hypothesized that half-dose alteplase would be associated with similar effectiveness compared to full-dose alteplase with a reduced risk of major bleeding.

Methods

Study Design

This was an observational cohort study evaluating patient data voluntarily submitted to the Premier Incorporated's Perspective™ database over a five-year period. The database includes information from over 700 U.S. hospitals with comprehensive billing, cost, device, medication and procedure data (19, 20). The study was approved by the Colorado Multiple Institutional Review Board.

Patient Population

Patients 18 years of age were included if they were admitted to the ICU on hospital day 1 or 2 between January 1, 2010 and December 31, 2014, with a primary diagnosis of pulmonary embolism (ICD-9 code 415.1), and treated with alteplase 50 mg or 100 mg intravenously as the initial thrombolytic strategy. Patient's receiving alteplase doses other than 50 mg or 100 mg, and those receiving catheter thrombus fragmentation as their first intervention for pulmonary embolism were not included. Patients were categorized into either half-dose (alteplase 50 mg IV) or full-dose (alteplase 100 mg IV) treatment groups based upon the first dose of alteplase administered.

Outcomes

The primary outcome evaluated in this study was treatment escalation, defined as initiation of vasopressors, need for secondary thrombolysis, assisted ventilation, embolectomy, catheter thrombus fragmentation, inferior vena cava filter placement, or cardiopulmonary resuscitation occurring after first alteplase administration (3). Secondary effectiveness outcomes included hospital mortality, readmission for pulmonary embolism, ICU length of stay, hospital length of stay, and total hospital charges. Safety outcomes were major bleeding (defined as a documented cerebral hemorrhage, gastrointestinal bleeding, acute blood loss anemia, administration of packed red blood cells, or administration of aminocaproic acid, tranexamic acid, or factor VIIa after alteplase administration) and documentation of a fibrinolytic therapy-related adverse event. Occurrence of an outcome was determined via pharmacy charge codes, current procedural terminology (CPT) codes, or ICD-9 codes as appropriate [Appendix A].

Data Analysis

Statistical analysis was performed (by author RR Allen) using methodology previous described by the Colorado Pulmonary Outcomes Research Group with minor modifications (21). Patient and hospital characteristics were compared between groups using the chi-

square test of Fisher's Exact test for categorical data and the unpaired t-test or Kruskal-Wallis test for continuous variables as appropriate. Description of propensity score matching and additional information relating to statistical methods, bias mitigation, and results validation via internal data are detailed in appendix A (22).

The propensity-score matched analysis adjusted for unbalanced covariates was the principal analysis for interpretation of study outcomes. Utilizing a 1:1 matched design and a treatment escalation rate of 41%, this study had more than 90% power to detect an absolute difference of 10% in the need for treatment escalation. All significance tests were 2-sided and a p-value < 0.05 was considered significant. All analyses were conducted using SAS version 9.3 (Cary, North Carolina).

Results

A total of 3,768 patients from 420 hospitals were included in the analysis, 3,069 (81.4%) in the full-dose group and 699 (18.6%) in the half-dose group (eFigure 1). Half-dose alteplase use increased from 16% of patients in 2010 to 20% of patients in 2014 (p=0.05). Overall, most patients were < 65 years old, 50% were male, 69% were Caucasian, and the predominant comorbidities were venous thromboembolism, hypertension, obesity, diabetes, cardiac arrhythmias, and fluid and electrolyte disorders (Table 1 and eTable 1). Patients were most commonly admitted to urban hospitals with greater than 500 beds located in the southern region of the US. Approximately 44% of patients were treated at teaching institutions.

Within 24 hours prior to alteplase administration, 36% were receiving vasopressor therapy, 26% invasive mechanical ventilation, and 11% non-invasive ventilation (Table 2). The majority of patients received alteplase therapy on hospital day 1 (median: hospital day 1; IQR 1–2 days). Patients receiving full-dose alteplase therapy had a similar number of elderly (> 65 or > 75 years old) patients (Table 1), but had more comorbidities, (e.g. hypertension, diabetes, heart failure, and pulmonary circulation disease) compared to patients in the half-dose alteplase group. Patients receiving full-dose alteplase were more likely to have a massive high-risk pulmonary embolism as indicated by increased use of vasopressor therapy, and had higher rates of mechanical ventilation and tests drawn to measure cardiac function (Table 2). The majority of patients received unfractionated heparin in addition to thrombolytic therapy; however, some transition between unfractionated heparin and low molecular weight heparin occurred. The median (IQR) total alteplase dose administered during hospitalization was 100 mg (100–100 mg) in the full-dose group and 50 mg (50–100 mg) in the half-dose group. In the patients (n=341) that received a second alteplase dose, the median time to the 2nd dose was one hospital day (IQR 1–1). The time to secondary thrombolysis was not different between treatment groups (p=0.67). In hospital mortality was 21% in the full-dose group compared to 12% in the half-dose group (p<0.01). The median hospital length of stay was shorter in the full-dose group (6 days, IQR 4–10 days) compared to the half-dose group (7 days, IQR 4–12 days), p<0.01.

Propensity Matched Analysis (Primary Analysis)

After propensity matching, 78% of patients in the half-dose group (N=548) were matched 1:1 with an equal number of patients in the full-dose group. Propensity matching successfully eliminated discordance amongst patient characteristics (eTable 2) and hospital characteristics, early therapies and tests (eTable 3).

The pre-specified primary outcome of treatment escalation occurred more frequently in patients receiving half-dose (54%) compared to full-dose alteplase (41%), $p < 0.01$ (Tables 3 and 4). Increased treatment escalation in the half-dose group was driven by greater need for additional thrombolysis and higher utilization of thrombosis fragmentation by catheter ($p < 0.01$ for both). There were no differences in the need for vasopressor therapy, assisted ventilation, embolectomy, cardiopulmonary resuscitation, or IVC filter placement ($p > 0.05$ for all). Half-dose alteplase was associated with increased hospital charges of approximately \$23,000 per patient (Table 4). Cerebral hemorrhage occurred in 0.5% and 0.4% of patients in the half-dose and full-dose groups respectively (Table 5). No differences in any type of major bleeding, need for reversal agents, or documented fibrinolytic related adverse events were observed.

Multivariate Analyses of the Entire Study Cohort

The total cohort (*i.e.* 3,768 patients) was analyzed after adjusting for the propensity to be treated with half-dose alteplase and differences in patient characteristics, admission year, comorbidities, hospital characteristics, early therapies and tests. Similar to the propensity matched analysis, this multivariate analysis showed that patients receiving full-dose therapy were less likely to require treatment escalation and was associated with a reduction in total hospitalization charges (Table 5). Conditional regression evaluating patient age, obesity, hypertension, renal failure, hepatic disease, anticoagulant use, and coagulopathy demonstrated similar results.

Subgroup Analyses of intermediate-risk pulmonary embolism patients

Primary and secondary outcome measures were evaluated in the intermediate-risk pulmonary embolism subgroup of patients by removing patients requiring vasopressor therapy and performing propensity matching among these patients. Patient and hospital characteristics are presented in eTables 4 and 5. In the propensity score matched analysis, treatment escalation was observed in 46% of the half-dose compared to 31% of the full-dose treated patients ($p < 0.01$). Hospital mortality rate was 5% in the half-dose group compared to 7% in the full-dose group ($p = 0.15$). Outcomes for the entire cohort and the propensity-matched cohort are presented in eTable 6. Similar to the entire cohort, treatment with half-dose alteplase for intermediate-risk pulmonary embolism was associated with more treatment escalation and an increased hospital charges, compared with full-dose alteplase. There were no differences in bleeding or documented fibrinolytic adverse effects between treatment groups.

Subgroup Analyses of high-risk pulmonary embolism patients

Evaluation of high-risk pulmonary embolism patients was completed using a propensity matched model including only patients requiring vasopressor therapy at the time of alteplase

administration. Patient and hospital characteristics are listed in eTables 7 and 8. In the propensity matched model, treatment escalation occurred in 83.1% of patients in each group ($p=0.99$). Vasopressor utilization was still required in 62% of half-dose patients and in 65% of full-dose patients the day after thrombolysis ($p=0.59$). A second dose of alteplase was administered to 18.6% of half-dose patients and 2.5% of full-dose patients ($p<0.01$). Hospital mortality was 40.7% in the half-dose group and 45.8% in the full-dose group ($p=0.43$). Half-dose alteplase was associated with an increased hospital charges, but no differences in clinical outcomes were observed (eTable 9). No differences in bleeding or fibrinolytic adverse effects were observed.

Subgroup analyses of patients without escalation of treatment

An analysis of patients receiving a single half-dose or full-dose alteplase administration without further escalation in treatment was conducted to evaluate the individual impact of alteplase treatment on clinical outcomes (eTables 10–11). No differences in hospital mortality were observed between half-dose and full-dose groups (6.2% vs. 7.7%; $p=0.05$, respectively). Cerebral hemorrhage occurred in 2 patients in the half-dose group and 1 patient in the full-dose group ($p=0.57$). Acute blood loss anemia occurred in 10 patients in each group ($p=0.99$) and documentation of a fibrinolytic causing an adverse event occurred in 1.8% and 2.2%, respectively ($p=0.76$). No differences in other clinical outcomes were observed (eTable 12).

Sensitivity Analysis of the Entire Cohort

When analyses were re-conducted to account for the rate of half-dose alteplase utilization at the hospital where they were admitted, results for hospital mortality was similar (Table 4). Consistent with the finding that half-dose therapy was associated with increased treatment escalation, for each 10% increase in the proportion of half-dose alteplase utilized by a hospital, the need for escalation of care is increased (Table 4). Results for the hierarchical analyses were not different from the propensity matched and multivariate models.

Discussion

This study demonstrates that half-dose alteplase is utilized as the initial treatment strategy over full-dose alteplase in approximately 19% of ICU patients with acute pulmonary embolism, and its use appears to be expanding as demonstrated by an increased proportional use from 2010 to 2014. Full-dose alteplase therapy appears favored by clinicians in patients with high-risk pulmonary embolism, with less than a quarter of patients in the half-dose group receiving vasopressors at the time of thrombolysis. Additionally, at the time of alteplase administration, patients treated with half-dose therapy were less likely to be receiving mechanical ventilation and less commonly evaluated via cardiac function tests. After propensity matching, the use of half-dose alteplase was associated with similar rates of in-hospital mortality and major bleeding compared to full-dose alteplase therapy; however, patients receiving half-dose alteplase were more likely to need further escalation in care for the management of their acute pulmonary embolism.

The overall observed in-hospital mortality in our study was 20%, which is similar to previous data including high-risk pulmonary embolism patients (23), and highlights the importance of management strategies to improve mortality in acute pulmonary embolism. After propensity score matching, there was no difference in mortality observed between half-dose and full-dose alteplase, suggesting that half-dose therapy produces similar survival rates in acute pulmonary embolism. However, this outcome is driven mostly by the 64% of study patients with intermediate-risk pulmonary embolism, where the mortality rate was lower at 5–7%. Studies to date have been unable to elucidate a significant effect of thrombolysis on mortality when compared to placebo in intermediate risk pulmonary embolism (3, 11). Similarly, the only study prospectively evaluating half-dose versus full-dose alteplase demonstrated similar mortality rates between treatment groups [2% (n=1) vs. 6% (n=3)] (17). Therefore, it is unlikely that any pragmatic study would be able to determine a significant difference on mortality due to alteplase dosing in this population. The infrequent use of half-dose alteplase in patients on vasopressor therapy limits the ability to draw firm conclusions regarding the impact of alteplase dosing on mortality in patients with high-risk pulmonary embolism. Due to the lack of severely ill (*e.g.* vasopressor treated) patients available for comparison from the half-dose cohort, fewer patients with high-risk pulmonary embolism were available for matching. Given the high rate of mortality in high-risk pulmonary embolism and the lack of conclusive data for half-dose therapy in this population, it seems most prudent to continue to recommend full-dose alteplase therapy in patients with hemodynamic decompensation due to acute pulmonary embolism.

Treatment escalation was common in both half-dose and full-dose alteplase treatment groups with more than 40% of patients requiring further advanced interventions to manage their acute pulmonary embolism. The need for treatment escalation is higher than reported in previous studies (10–25%) and likely reflects the inclusion of patients with high-risk pulmonary embolism (*e.g.* higher rates of vasopressor use) and our addition of inferior vena cava filter placement to the criteria (3). Treatment escalation was more common in patients receiving half-dose alteplase therapy and was driven by the more frequent administration of a second alteplase dose or the use of thrombosis fragmentation by catheter. The lack of differences between treatment groups in the need for vasopressors, assisted ventilation, cardiopulmonary resuscitation, and IVC filter placement after the first dose of alteplase makes it difficult to elucidate whether secondary thrombolysis and thrombosis fragmentation by catheter was pre-planned or as a result of patient decompensation. Previous studies have shown comparable improvements in echocardiographic findings or right heart strain and perfusion scans with half-dose versus full-dose alteplase therapy (17, 18). Half-dose alteplase therapy has also demonstrated effectiveness in reducing pulmonary hypertension acutely after administration (6). There has been some suggestion that half-dose therapy may be most reasonable in patients with lower body weight (<65 kg) and those at higher risk of bleeding (17, 24). In our study, both treatment approaches yielded similar mortality, but escalation of care in the half-dose group was associated with a substantially increased hospital charges (~\$25,000 increase per patient).

Half-dose and full dose alteplase were associated with similar rates of major bleeding. Of the 3,768 patients treated with alteplase therapy, cerebral hemorrhage occurred in 18 patients (0.5%), which is consistent with previous studies of alteplase for acute pulmonary embolism

(3, 6, 11). Documentation of acute blood loss anemia, and the administration of packed red blood cells or antifibrinolytic agents after alteplase administration was similar between treatment groups. Our findings are contrary to previous studies that suggest that lower doses of alteplase may significantly reduce bleeding (6, 17). In a previous study of 118 patients evaluating half-dose versus full-dose alteplase therapy, major bleeding occurred in 3% of half-dose compared to 10% of full-dose treated patients ($p=0.29$) (17). It is possible that the similar rates of major bleeding observed between treatment groups in our study are due to patient selection. Patients with a higher perceived risk of bleeding may have preferentially been given half-dose alteplase therapy as a more conservative strategy. However, we did not observe any preferential use of half-dose alteplase therapy in patients with increased bleeding risk, such as those greater than 65 years old, or those with renal or hepatic dysfunction, cancer, or coagulopathies. It is possible that other unidentified bleeding risk factors were present in the half-dose group; and if so, one may conclude that utilizing half-dose therapy in these patients may result in similar bleeding rates to full-dose alteplase therapy. Although it is reasonable to assume that utilizing a lower dose of alteplase will reduce the risk of bleeding in a dose-dependent manner, currently no comparative evidence has demonstrated that lower dose alteplase significantly reduces major bleeding or the incidence of intracranial hemorrhage in patients with acute pulmonary embolism. Therefore, the use of the term “safe” dose thrombolysis to describe half-dose therapy should be avoided. This is especially true since our study found that half-dose alteplase was associated with higher rates of secondary thrombolysis and catheter fragmentation, therapies that carry additional risks.

Several limitations should be considered when interpreting the results of this study due to its observational design. We were not able to determine why a particular thrombolytic treatment strategy was chosen in the study patients or assess utilization of hospital based treatment protocols. Patient body weight was unavailable in the database, so evaluation of weight-based dosing on effectiveness and safety outcomes was not possible. Vital signs, echocardiographic, and laboratory results are not available within the database, so differentiation of high-risk and intermediate-risk pulmonary embolism was conducted based upon vasopressor usage at the time of alteplase administration. Additionally, this limited our ability to evaluate treatment strategies by the more contemporary definitions of low, intermediate, and high risk PE subgroups. Our analysis of major bleeding is limited to the availability of specific diagnostic codes and the use of rescue pharmacologic therapy, which limits our analysis to only certain types of major bleeding. Additionally, we were unable to measure the incidence of minor bleeding or long-term outcomes. Hospital costs may be reflective of a variety of patient and hospital factors and actual differences due to alteplase treatment may not be fully explained by the data. Although rigorous statistical methods were utilized, including propensity score matching and covariate adjustment, it is possible that residual biases remain.

Conclusions

Our data suggest that initiating treatment with half-dose alteplase for pulmonary embolism is much less common than utilization of full-dose therapy, but its use appears to be increasing. Mortality between thrombolysis treatment strategies were similar and

approximately 46% of patients treated with half-dose therapy did not require further intervention. However, in comparison to full-dose therapy, escalation of care occurs more frequently. Additionally, no clear differences in major bleeding (most notably intracerebral hemorrhage) or adverse events occurred between half-dose and full-dose therapy. Preferably, a prospective clinical trial should be performed to determine the optimum alteplase dose that maximizes benefits and minimizes the risk of bleeding, particularly for patients with intermediate-risk pulmonary embolism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Patient Characteristics

Patient Characteristics	Alteplase 50mg (N=699)		Alteplase 100mg (N=3,069)		p-value
	n	%	n	%	
Age					
18–29	44	6.3%	155	5.1%	
30–39	64	9.2%	225	7.3%	
40–49	111	15.9%	433	14.1%	
50–59	135	19.3%	640	20.9%	0.04
60–69	162	23.2%	769	25.1%	
70–79	108	15.5%	555	18.1%	
80–89	69	9.9%	284	9.3%	
Age > or 65 years					
65	452	64.7%	1,943	63.3%	
>65	247	35.3%	1,126	36.7%	0.50
Age > or 75 years					
75	599	85.7%	2,592	84.5%	
>75	100	14.3%	477	15.5%	0.41
Sex					
Males	363	51.9%	1,526	49.7%	
Females	336	48.1%	1,543	50.3%	0.29
Race					
White	486	69.5%	2,123	69.2%	
Black	102	14.6%	537	17.5%	
Hispanic	5	0.7%	18	0.6%	0.14
Other	106	15.2%	391	12.7%	
Primary Insurance					
Medicare	263	37.6%	1,349	44.0%	
Medicaid	83	11.9%	272	8.9%	
Private	274	39.2%	1,062	34.6%	0.002
Self Pay/Other	79	11.3%	386	12.6%	

Patient Characteristics		Alteplase 50mg (N=699)		Alteplase 100mg (N=3,069)		p-value
		n	%	n	%	
Admission Year						
2010		95	13.6%	502	16.4%	0.04
2011		110	15.7%	572	18.6%	
2012		142	20.3%	628	20.5%	
2013		184	26.3%	690	22.5%	
2014		168	24.0%	677	22.1%	
Comorbidities ^a						
Hypertension		378	54.1%	1,859	60.6%	<0.01
Deficiency anemias		128	18.3%	521	17.0%	0.40
Chronic pulmonary heart disease		115	16.5%	618	20.1%	0.03
Coagulopathy		76	10.9%	319	10.4%	0.71
Venous thromboembolism		443	63.4%	1,552	50.6%	<0.01

Data are presented as proportions.

^a A full list of comorbidities evaluated and results can be found in eTable 1

Table 2

Hospital Characteristics, Early Therapies and Tests

Hospital Characteristics, Early Therapies and Tests	Alteplase 50mg (N=699)		Alteplase 100mg (N=3,069)		p-value
	n	%	n	%	
Number of Beds					
<200	55	7.9%	422	13.8%	<0.01
200–300	93	13.3%	575	18.7%	
301–400	125	17.9%	678	22.1%	
401–500	85	12.2%	454	14.8%	
>500	341	48.8%	940	30.6%	
Patient Population					
Urban	645	92.3%	2,708	88.2%	<0.01
Rural	54	7.7%	361	11.8%	
Region					
South	424	60.7%	1,609	52.4%	<0.01
Midwest	89	12.7%	450	14.7%	
Northeast	59	8.4%	462	15.1%	
West	127	18.2%	548	17.9%	
Teaching Status					
Nonteaching	331	47.4%	1,777	57.9%	<0.01
Teaching	368	52.6%	1,292	42.1%	
Early therapies and tests					
Vasopressor Therapy	163	23.3%	1,208	39.4%	<0.01
Mechanical Ventilation	100	14.3%	875	28.5%	<0.01
Noninvasive Ventilation	64	9.2%	336	10.9%	0.17
Arterial Blood Gas	56	8.0%	427	13.9%	<0.01
Brain Natriuretic Peptide	248	35.5%	1,576	51.4%	<0.01
Loop diuretics (furosemide, bumetanide, or torsemide)	121	17.3%	479	15.6%	0.27
CT Pulmonary Angiography	566	81.0%	2,444	79.6%	0.43
Troponin Test	394	56.4%	2,525	82.3%	<0.01
Echocardiography	384	54.9%	2,296	74.8%	<0.01

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Hospital Characteristics, Early Therapies and Tests	Alteplase 50mg (N=699)		Alteplase 100mg (N=3,069)		p-value
	n	%	n	%	
Unfractionated Heparin	633	90.6%	2,538	82.7%	<0.01
Low Molecular Weight Heparin	258	36.9%	1,061	34.6%	0.24
Direct-acting oral anticoagulants (rivaroxaban, apixaban, dabigatran, edoxaban)	16	2.3%	74	2.4%	0.83

Data are presented as proportions.

Table 3

Patient Outcomes

Outcomes	Unadjusted				Matched			
	50 mg (N=699)	100 mg (N=3,069)	n	%	50 mg (N=548)	100 mg (N=548)	n	%
Escalation of treatment								
Initiation of vasopressor after first alteplase administration	379	54.2%	1,448	47.2%	295	53.8%	227	41.4%
Secondary thrombolysis	105	15.0%	930	30.3%	94	17.2%	99	18.1%
Initiation of assisted ventilation after first alteplase administration	196	28.0%	145	4.7%	142	25.9%	40	7.3%
Embolectomy after first alteplase administration	77	11.0%	330	10.8%	65	11.9%	54	9.9%
Thrombosis fragmentation by catheter after first alteplase administration	11	1.6%	14	0.5%	9	1.6%	6	1.1%
Cardiopulmonary resuscitation after first alteplase administration	85	12.2%	86	2.8%	78	14.2%	21	3.8%
IVC filter placement after first alteplase administration	47	6.7%	396	12.9%	43	7.8%	53	9.7%
Readmitted for pulmonary embolism	111	15.9%	350	11.4%	86	15.7%	77	14.1%
In hospital mortality	41	5.9%	252	8.2%	35	6.4%	40	7.3%
Readmission within 30 days of discharge	82	11.7%	656	21.4%	71	13.0%	83	15.1%
	29	4.1%	90	2.9%	23	4.2%	19	3.5%

Outcomes	Unadjusted				Matched			
	50 mg (N=699)	100 mg (N=3,069)	p-value	Median (IQR)	50 mg (N=548)	100 mg (N=548)	p-value	Median (IQR)
Time to Next Readmission (days)	87.0 (25, 294)	126 (23, 388)	0.15	83.0 (24.0, 249.0)	110.0 (15.0, 405.0)	0.66		
Hospital length of stay (days)	7 (4, 12)	6 (4, 10)	<0.01	7.0 (4.0, 12.0)	7.0 (4.0, 10.0)	0.15		
ICU length of stay (days)	2 (1, 4)	2 (1, 4)	0.02	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	0.18		
Total cost (US \$)	\$108,897 (\$69,417, \$160,893)	\$76,879 (\$49,867, \$127,902)	<0.01	\$103,843 (\$67,785, \$160,075)	\$76,495 (\$52,201, \$127,537)	<0.01		

Data are presented as proportions or median, interquartile range (IQR).

Table 4

Primary and Secondary Outcomes for half-dose vs. full-dose alteplase

Outcomes	Models for Primary Cohort							
	Total Cohort		Total Cohort		Propensity-matched Cohort (Primary Analysis)			
	Unadjusted(N=3,768)		Propensity score and covariate adjustment ^a (N=3,768)		Matched sample adjusted for unbalanced covariates ^b (N=1,096)		Group Treatment for 10% Increase in Hospital Proportion of Half-dose Alteplase administered ^a	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Treatment Escalation	1.33 (1.05–1.67)	0.02	2.02 (1.51–2.71)	< 0.01	1.65 (1.25–2.18)	< 0.01	1.07 (1.02–1.13)	0.01
Hospital Mortality	0.49 (0.34–0.70)	< 0.01	0.73 (0.48–1.11)	0.14	0.83 (0.56–1.24)	0.37	0.98 (0.91–1.05)	0.52
	Linear Regression Coefficient (95% CI)	p value	Linear Regression Coefficient (95% CI)	p value	Linear Regression Coefficient (95% CI)	p value		
ICU LOS (d)	–0.40 (–0.98, 0.17)	0.17	–0.26 (–0.69, 0.16)	0.22	–0.43 (–1.09, 0.22)	0.20		
Hospital LOS (d)	0.83 (0.09, 1.57)	0.03	0.50 (–0.24, 1.23)	0.18	0.58 (–0.39, 1.54)	0.24		
Total Cost (\$)	27,604 (11,179, 44,030)	< 0.01	20,263 (4,880, 35,645)	< 0.01	23,223 (5,642, 40,804)	< 0.01		

OR < 1, or regression coefficient < 0, demonstrates benefit towards treatment with half-dose alteplase

Abbreviations: Length of stay (LOS); Intensive care unit (ICU)

^a All covariates from Tables 1 and 2 included in models with the exception of variables with too few patients (HIV/AIDS)^b Unbalanced covariates: None

Table 5

Potential Thrombolytic Adverse Events

Reported Adverse Events	Unadjusted			Matched		
	50 mg (N=699) n (%)	100 mg (N=3,069) n (%)	p-value	50 mg (N=548) n (%)	100 mg (N=548) n (%)	p-value
Cerebral hemorrhage	4 (0.6%)	14 (0.5%)	0.70	3 (0.5%)	2 (0.4%)	0.67
GI hemorrhage	13 (1.9%)	67 (2.2%)	0.58	9 (1.6%)	9 (1.6%)	0.97
Hemoptysis	1 (0.1%)	3 (0.1%)	0.75	1 (0.2%)	0 (0.0%)	NS
Acute blood loss anemia	49 (7.0%)	184 (6.0%)	0.34	38 (6.9%)	25 (4.6%)	0.11
Fibrinolytic causing adverse event	12 (1.7%)	61 (2.0%)	0.62	11 (2.0%)	9 (1.7%)	0.68
Anticoagulant causing adverse event	16 (2.3%)	74 (2.4%)	0.83	14 (2.6%)	15 (2.8%)	0.82
Administration of Packed Red Blood Cells after alteplase	20 (2.9%)	131 (4.3%)	0.09	18 (3.3%)	23 (4.2%)	0.43
Administration of aminocaproic acid after alteplase	5 (0.7%)	7 (0.2%)	0.05	4 (0.7%)	0 (0.0%)	NS
Administration of tranexamic acid after alteplase	1 (0.1%)	3 (0.1%)	0.74	0 (0.0%)	2 (0.4%)	0.99
Administration of factor VII after alteplase	9 (1.3%)	25 (0.8%)	0.24	6 (1.1%)	6 (1.1%)	0.99

Data are presented as N (%).