# Safety and Efficacy of Reduced-Dose Versus Full-Dose Alteplase for Acute Pulmonary Embolism: A Multicenter Observational Comparative Effectiveness Study



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**OBJECTIVES:** Systemic thrombolysis improves outcomes in patients with pulmonary embolism (PE) but is associated with the risk of hemorrhage. The data on efficacy and safety of reduced-dose alteplase are limited. The study objective was to compare the characteristics, outcomes, and complications of patients with PE treated with full- or reduced-dose alteplase regimens.

**DESIGN:** Multicenter retrospective observational study.

**SETTING:** Tertiary care hospital and 15 community and academic centers of a large healthcare system.

**PATIENTS:** Hospitalized patients with PE treated with systemic alteplase.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** Pre- and post-alteplase hemodynamic and respiratory variables, patient outcomes, and complications were compared. Propensity score (PS) weighting was used to adjust for imbalances of baseline characteristics between reduced- and full-dose patients. Separate analyses were performed using the unweighted and weighted cohorts. Ninety-eight patients were treated with full-dose (100 mg) and 186 with reduced-dose (50 mg) regimens. Following alteplase, significant improvements in shock index, blood pressure, heart rate, respiratory rate, and supplemental oxygen requirements were observed in both groups. Hemorrhagic complications were lower with the reduced-dose compared with the full-dose regimen (13% vs. 24.5%, $p = 0.014$), and most were minor. Major extracranial hemorrhage occurred in 1.1% versus 6.1%, respectively ($p = 0.022$). Complications were associated with supratherapeutic levels of heparin anticoagulation in 37.5% of cases and invasive procedures in 31.3% of cases. The differences in complications persisted after PS weighting (15.4% vs. 24.7%, $p = 0.12$ and 1.3% vs. 7.1%, $p = 0.067$), but did not reach statistical significance. There were no significant differences in mortality, discharge destination, ICU or hospital length of stay, or readmission after PS weighting.

**CONCLUSIONS:** In a retrospective, PS-weighted observational study, when compared with the full-dose, reduced-dose alteplase results in similar outcomes but fewer hemorrhagic complications. Avoidance of excessive levels of anticoagulation or invasive procedures should be considered to further reduce complications.

**KEYWORDS:** anticoagulants; hemorrhage; outcome assessment; pulmonary thromboembolism; tissue plasminogen activator

Pulmonary embolism (PE) remains a significant cause of morbidity and mortality that can range from 8.1% in stable patients to 25% in those presenting with signs of shock, and to 65% in those requiring cardiopulmonary resuscitation (CPR), with long-term mortality to a significant



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## KEY POINTS

**Question:** What are the differences in characteristics, outcomes, and complications in pulmonary embolism patients treated with full- or reduced-dose systemic thrombolysis regimens?

**Findings:** Following alteplase administration, significant improvements in hemodynamic and respiratory parameters were noted in both groups. There was no difference between the groups in mortality, discharge destination, ICU or hospital length of stay, or readmission rates. Rates of hemorrhagic complications were lower in the reduced-dose as compared with the full-dose group.

**Meaning:** In a retrospective, propensity score-weighted observational study, reduced-dose alteplase was as effective as the full-dose regimen but was associated with a lower risk of bleeding.



degree linked to medical comorbidities (1, 2). Chronic thromboembolic pulmonary hypertension related to acute symptomatic PE occurs in 0.4–6.2% of cases and can lead to right heart failure and death (3). Systemic thrombolysis has been shown to improve outcomes in massive (high-risk) PE characterized by hemodynamic instability (4, 5). It may also benefit selected submassive (intermediate risk) PE patients without hypotension or shock but with evidence of right ventricular (RV) dysfunction, positive biomarkers, and clinical signs of decompensation (6–8). However, thrombolysis can be associated with bleeding, including intracranial hemorrhage (ICH) (9). In meta-analyses of clinical trials comparing systemic thrombolysis to anticoagulation alone, thrombolytics were associated with lower rates of all-cause mortality and recurrent PE but greater risks of bleeding complications (10, 11). There is significant variability in the reported bleeding rates. A randomized controlled trial comparing heparin plus alteplase versus heparin alone in normotensive PE patients with RV dysfunction showed decreased need for escalation of care due to hemodynamic decompensation in the alteplase group and minimal bleeding complications, which were similar in the treatment and control groups, with no fatal or ICH events (12). A more recent trial comparing weight-adjusted tenecteplase plus heparin versus heparin alone in patients with intermediate-risk PE confirmed benefit of systemic thrombolysis, but the risk of complications was significantly higher in the tenecteplase group, with an 11.5% rate of major bleeding and 2% frequency of ICH (13). The complication rate variability suggests that the thrombolytic dose regimen and possibly other factors, such as intensity of concomitant anticoagulation may affect the risk of hemorrhage.

The full-dose alteplase regimen consisting of 100 mg administered intravenously over 2 hours was associated with an angiographic improvement, significant reduction in PE-induced pulmonary hypertension, and improved pulmonary perfusion in a randomized trial comparing alteplase with urokinase, and with improvement in RV function and pulmonary perfusion when alteplase plus heparin were compared with heparin alone (14–16). The reduced-dose regimen (50 mg) was compared with a full-dose alteplase in a randomized trial of 118 PE patients with hemodynamic instability or massive pulmonary artery obstruction. Improvements in RV dysfunction, lung perfusion defects, and pulmonary artery obstructions were similar in both groups, but the reduced-dose regimen resulted in less bleeding (3% vs. 10%), especially in patients with a body weight less than 65 kg (17). Another trial randomized moderate PE patients to 50 mg alteplase dose plus anticoagulation or anticoagulation alone. The endpoints of pulmonary hypertension and recurrent PE were less prevalent in the thrombolysis group, and no bleeding complications occurred in either group (18). A retrospective study comparing ultrasound-facilitated catheter-directed thrombolysis to systemic reduced-dose alteplase demonstrated similar improvements in pulmonary artery pressures and RV size with a significantly lower cost of treatment in the systemic thrombolysis group (19). However, a retrospective database study comparing reduced- versus full-dose alteplase in propensity-matched patients with PE found increased need for secondary thrombolysis and catheter thrombus fragmentation in the reduced-dose group, whereas there was no difference in mortality or complications (20). Given the small number of studies and the variability of the trial size, patient enrollment criteria, and reported outcomes, additional information is needed to inform clinicians on the optimal thrombolytic dose regimen and factors associated with bleeding complications.

This multicenter observational study aimed to compare baseline characteristics, outcomes, and complications in patients with PE treated with full- or reduced-dose alteplase regimens.



## MATERIALS AND METHODS

This was a retrospective observational study of patients discharged from Abbott Northwestern Hospital (a tertiary care center in Minneapolis, Minnesota) and Mayo Health System (15 community and academic centers) between January 1, 2012, and December 31, 2020. Patients were included if they were 18 years old or older and treated with systemic (IV) alteplase for PE. Exclusion criteria included absence of authorization for use of electronic health records for research purposes and alteplase administration in the setting of cardiac arrest, or patients treated with extracorporeal membrane oxygenation. Data for the study were collected both via data extraction from the electronic health records as well as chart review for variables difficult to extract such as comorbid conditions, invasive procedures, and complications. Both extracted and chart review data were entered into Research Electronic Data Capture. Each case with hemorrhagic complication was reviewed by two independent researchers to understand the circumstances and factors contributing to the complication development, and their findings were adjudicated. The study was determined to be exempt from review by both the relevant institutional review boards (IRB 1804450; IRB 21-011394).

### Measures

Patients were classified as receiving either full dose alteplase if they received 100 mg IV over 2 hours, or reduced dose alteplase if they received 50 mg IV over 2 hours or 10 mg bolus over 1 minute followed by 40 mg over 2 hours.

Primary outcomes for this study were all-cause and PE-related mortality or hemorrhage within 7 days of alteplase administration. PE-related deaths were defined as those due to PE as the primary cause. Major extracranial hemorrhage was defined as fatal bleeding, and/or bleeding in a critical area or organ, such as intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of RBCs (21). ICH was defined as any degree of subarachnoid, subdural, or intraparenchymal bleeding. Minor hemorrhage was defined as any bleeding not meeting major extracranial or ICH criteria.

Secondary outcomes included shock index at 8 hours after alteplase administration defined as HR divided by systolic blood pressure (SBP), 30-day and 1-year all-cause mortality, and ICU and hospital length of stay (LOS). Other key secondary outcomes included changes in SBP, heart rate (HR), respiratory rate (RR), need for supplemental oxygen (oxygen), noninvasive ventilation, mechanical ventilator, and vasopressor use before and after alteplase.

Measures before alteplase were defined as the nadir SBP, peak HR, peak RR, and nadir $Spo_2$, within 8 hours before alteplase administration. Similarly, the post-alteplase measures were nadir SBP, peak HR, peak RR, and nadir Sp $o_2$ at approximately 8 hours after alteplase administration.

Pre-alteplase echocardiogram was defined as echocardiogram obtained during index hospitalization before alteplase administration. Post-alteplase echocardiogram was defined as first available echocardiogram following alteplase administration. Echocardiographic measures included global assessment of RV function categorized as normal or severe, moderate, or mild dysfunction; tricuspid regurgitation pressure gradient (TRPG), and tricuspid annular plane systolic excursion (TAPSE).

Patient baseline measures included age, gender, weight (kg), and body mass index. PE severity was defined as massive (PE-related hypotension or shock) or submassive (presence of RV dysfunction and/or abnormal troponin or brain natriuretic peptide (BNP) without hypotension or shock) (22). Medical history included smoking status (current, former, never), and history of specific medical events or comorbidities: PE/deep venous thrombosis, cancer, congestive heart failure, chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, obstructive sleep apnea, coronary artery disease, hypertension, chronic kidney disease. Baseline measures at admission related to disease severity and treatment included syncope within 7 days prior, need for CPR, abnormal troponin, BNP, and lactate (defined as above the upper limit of normal in the corresponding hospital laboratory). Sequential Organ Failure Assessment (SOFA) scores were

calculated using information in the record at the time of admission (23). Antiplatelet and anticoagulant use were measured for the 7 days before alteplase start; additionally, trauma or invasive procedures were documented for the 30 days before treatment.

Although heparin protocols evolved over the course of years and were site-specific, the common approach included initiation of unfractionated heparin infusion at the guideline-recommended dose at the time of PE diagnosis and titration to a heparin anti-Xa of 0.3–0.7 IU/mL or a correlated activated partial thromboplastin time (aPTT) range (24). Supratherapeutic anticoagulation was defined as aPTT greater than 2.5 times of control value or heparin activity greater than 0.7 units/mL.

## Statistical Analysis

Due to the observational nature of this study, propensity score (PS) weighting was used to adjust for imbalances of baseline characteristics between reduced- and full-dose patients. The PS was defined as the probability of a patient receiving a reduced-dose of alteplase given a set of baseline covariates (variables summarized in **Fig. 1**) as estimated by logistic regression. The weights used for analysis were defined to be 1/PS for those who received reduced-dose alteplase, and 1/(1-PS) for those who received full-dose alteplase. The weights in each group were then divided by the mean weight of that respective group, so the sum of the weights was equal to the original sample size of each group.

We assessed covariate imbalance between the full and reduced-dose groups by evaluating the standardized difference for each baseline covariate. The standardized difference for a continuous covariate was defined as the absolute difference in group means divided by an estimate of the pooled SD. The derivation was similar for nominal covariates. A standardized

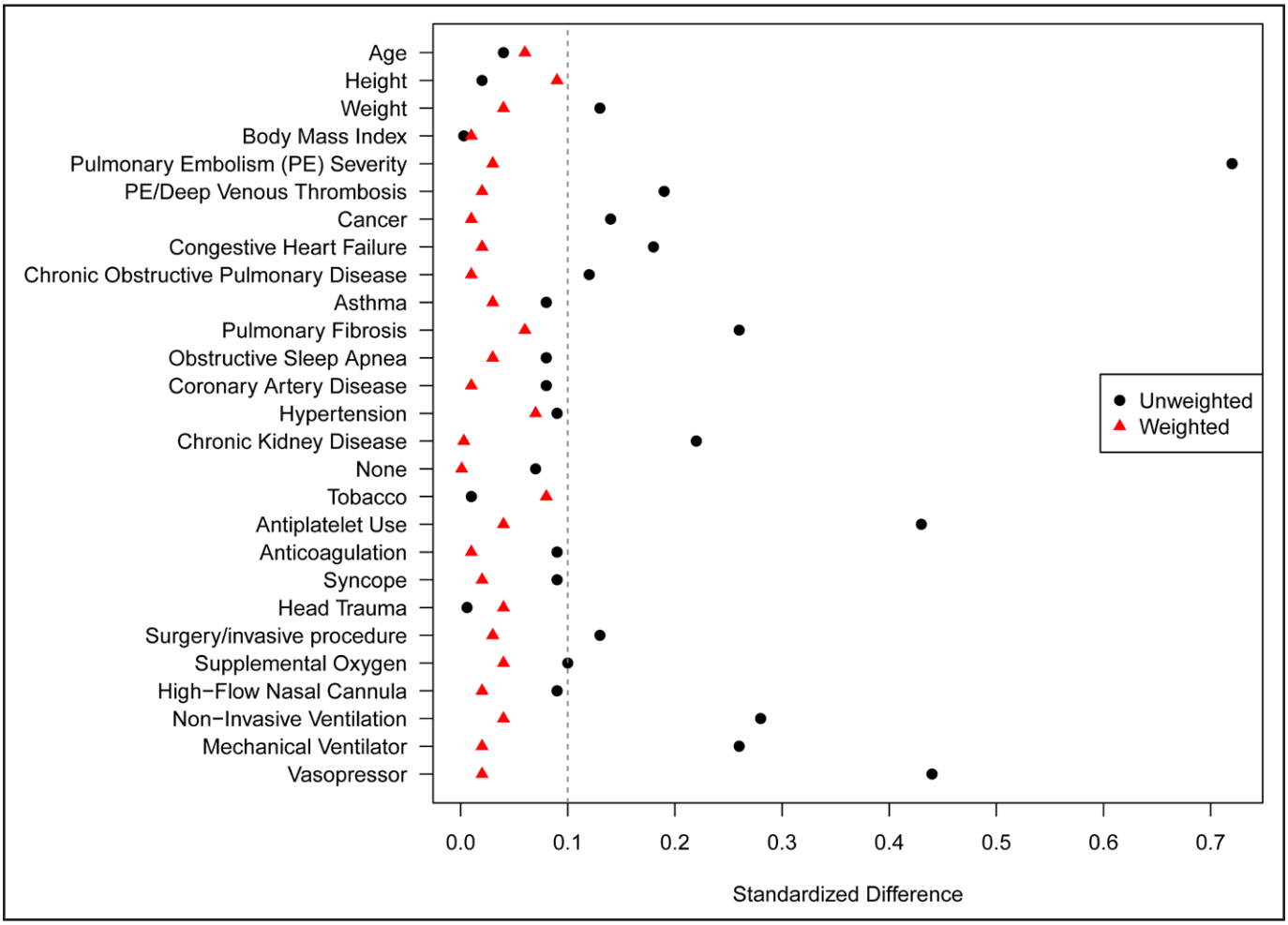


**Figure 1.** Standardized differences (absolute value) for variables used in the propensity scores (PSs) derivation in the unweighted and PS-weighted cohorts.

difference of less than 0.10 denotes negligible covariate imbalance between groups.

Separate analyses were performed using the unweighted and weighted cohorts. Continuous variables were compared between dosing groups using either a *t*-test or Wilcoxon rank sum test, and categorical variables were compared using a Chi-square test. A multivariable logistic regression model was used to assess the association between dose group and hemorrhagic complications after adjusting for age (≥ 75 vs. < 75), weight (≥ 65 kg vs. < 65 kg), if an invasive procedure was performed in the 30 days before alteplase, and if the patient received an antiplatelet agent within the 7 days before alteplase. Weighted versions of these analyses were used to assess these associations in the weighted cohort. All calculated *p* values were two-sided and *p* values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS, version 9.4 software (SAS Institute, Cary, NC).



# RESULTS

## Cohort Characteristics

A total of 284 patients were included in the retrospective analysis; 98 were treated with the full-dose and 186 with the reduced-dose alteplase regimen. At baseline, PE was classified as massive in 97 (34.5%) and submassive in 184 (65.5%) cases (**Table 1**). Patients receiving the full-dose regimen were more likely to have a massive PE relative to those in the reduced-dose group (56.1% vs. 23%), whereas the reduced-dose group had a higher proportion of patients with a submassive PE (77.0% vs. 43.9%), $p < 0.001$. There were no clinically significant differences between the groups in terms of age and gender, comorbidities, or most baseline laboratory values. Most patients in both groups had elevated troponin and BNP and were receiving systemic anticoagulation before thrombolysis. Before the PS weighting, abnormal lactate, use of antiplatelet agents, and the need for CPR were all more common in the full-dose alteplase group (Table 1). Additionally, patients treated with the full-dose regimen had significantly lower SBP (94.2 vs. 108.8 mm Hg), higher peak HR (119.8 vs. 111.1 beats/min), higher peak RR (29.9 vs. 25.4), higher SOFA score (3 vs. 2, $p = 0.003$), and more patients in this group required noninvasive ventilation (18.8% vs. 9.3%, $p = 0.023$), mechanical ventilation (13.5% vs. 5.9%, $p = 0.031$), vasopressor support (27.6% vs. 10.8%, $p < 0.001$), and CPR (7.1% vs. 2.2%, $p = 0.038$) (**Table 2**).

After the PS weighting, the full-and reduced-dose alteplase groups appeared well balanced with regard to key baseline differences in the unweighted groups: PE severity, need for CPR, antiplatelet use, mechanical ventilation, and vasopressors (all standardized differences < 0.10, indicating negligible imbalance). After weighting we still saw significant differences in the percentage with abnormal lactate (but with a reduced difference), shock index, and RR (Fig. 1 and Tables 1 and 2).

## Outcomes

In the weighted cohort, there was no difference between the groups in 7-day all-cause (5.6% in full-dose vs. 8% in reduced-dose, $p = 0.45$) or PE-related (4% in full-dose vs. 4.2% in reduced-dose, $p = 0.93$) mortality, nor in 30-day or 1-year mortality. Following alteplase administration, improvements in SBP, HR, shock index, RR, and supplemental oxygen requirements were noted in both groups, and there was significant decrease in the noninvasive ventilation requirements in the reduced-dose group. The need for rescue interventions (catheter-directed procedures or surgical embolectomy) was infrequent and did not differ between groups. There were no significant differences between the groups in the discharge destination, ICU or hospital LOS, or readmission rates (Table 2).

No significant outcome differences related to the alteplase dose were noted when massive and submassive PE subgroups were analyzed separately. Mortality was substantially higher in patients with massive PE as compared to patients with submassive PE (17.5% all-cause and 10.3% PE-related in massive vs. 1.1% and 0.5%, respectively, in submassive PE subgroup), with the differences persisting after PS weighting (**Table 3**).

Among cases with available echocardiogram results, global RV function before thrombolysis was described as severely abnormal in 56.5% and 44.5% of patients treated with full-dose and reduced-dose alteplase, and these rates decreased to 7.4% and 7.3%, respectively, following the treatment. Improvements in the TAPSE and TRPG were also noted (**Supplemental Table 1**, http://links.lww.com/CCM/H473).

# TABLE 1.
## Baseline Characteristics of Patients With Pulmonary Embolism Treated With Systemic Thrombolysis

| | Unweighted Cohort | | | | Weighted Cohort | | |
|---|---|---|---|---|---|---|---|
| | Total ($n = 284$) | Full Dose ($n = 98$) | Reduced Dose ($n = 186$) | $p$ | Full Dose ($n = 98$) | Reduced Dose ($n = 186$) | $p$ |
| Age, mean (SD) | 60.7 (15.1) | 60.4 (14.7) | 60.9 (15.3) | 0.93 | 59.7 (14.9) | 60.5 (15.9) | 0.66 |
| Gender, male | 156 (54.9%) | 55 (56.1%) | 101 (54.3%) | 0.77 | 56.8% | 52.8% | 0.52 |
| Weight, kg, median (IQR) | 100.9 (85.5, 124.6) | 98.8 (85.1, 117.9) | 101.6 (86.8, 127.5) | 0.26 | 102.2 (87.0, 114.5) | 100.7 (84.7, 125.3) | 0.77 |
| Body mass index median (IQR) | 33.7 (29.1, 40.7) | 33.3 (28.1, 40.5) | 33.9 (29.2, 40.9) | 0.37 | 34.2 (28.4, 38.6) | 33.5 (28.9, 40.7) | 0.94 |
| Pulmonary embolism severity | | | | < 0.001 | | | 0.84 |
| Massive | 97 (34.5%) | 55 (56.1%) | 42 (23.0%) | | 36.4% | 35.0% | |
| Submassive | 184 (65.5%) | 43 (43.9%) | 141 (77.0%) | | 63.6% | 65.0% | |
| Medical history | | | | | | | |
| Pulmonary embolism/deep venous thrombosis | 69 (24.3%) | 29 (29.6%) | 40 (21.5%) | 0.13 | 24.8% | 24.1% | 0.91 |
| Cancer | 56 (19.7%) | 23 (23.5%) | 33 (17.7%) | 0.25 | 21.0% | 20.7% | 0.96 |
| Congestive heart failure | 35 (12.3%) | 16 (16.3%) | 19 (10.2%) | 0.14 | 11.1% | 11.9% | 0.85 |
| Chronic obstructive pulmonary disease | 33 (11.6%) | 14 (14.3%) | 19 (10.2%) | 0.31 | 10.1% | 10.3% | 0.94 |
| Asthma | 41 (14.4%) | 16 (16.3%) | 25 (13.4%) | 0.51 | 14.6% | 13.5% | 0.82 |
| Pulmonary fibrosis | 31 (10.9%) | 16 (16.3%) | 15 (8.1%) | 0.034 | 11.8% | 9.9% | 0.65 |
| Obstructive sleep apnea | 80 (28.2%) | 30 (30.6%) | 50 (26.9%) | 0.51 | 25.7% | 27.0% | 0.83 |
| Coronary artery disease | 52 (18.3%) | 20 (20.4%) | 32 (17.2%) | 0.51 | 18.8% | 18.4% | 0.95 |
| Hypertension | 173 (60.9%) | 57 (58.2%) | 116 (62.4%) | 0.49 | 56.6% | 59.8% | 0.66 |
| Chronic kidney disease | 43 (15.1%) | 20 (20.4%) | 23 (12.4%) | 0.072 | 14.9% | 14.9% | 0.98 |
| None | 50 (17.6%) | 19 (19.4%) | 31 (16.7%) | 0.57 | 17.5% | 17.6% | 0.99 |
| Tobacco | | | | 0.94 | | | 0.85 |
| Current | 25 (8.9%) | 8 (8.2%) | 17 (9.2%) | | 7.8% | 8.5% | |
| Past | 67 (23.8%) | 24 (24.7%) | 43 (23.2%) | | 20.9% | 23.8% | |
| Never | 190 (67.4%) | 65 (67.0%) | 125 (67.6%) | | 71.3% | 67.7% | |

(*Continued*)

## TABLE 1. (*Continued*)

**Baseline Characteristics of Patients With Pulmonary Embolism Treated With Systemic Thrombolysis**

| | Unweighted Cohort | | | | Weighted Cohort | | |
|---|---|---|---|---|---|---|---|
| | Total (*n* = 284) | Full Dose (*n* = 98) | Reduced Dose (*n* = 186) | *p* | Full Dose (*n* = 98) | Reduced Dose (*n* = 186) | *p* |
| Syncope within 7 d before alteplase | 46 (16.3%) | 18 (18.4%) | 28 (15.1%) | 0.48 | 15.8% | 16.4% | 0.90 |
| Need for cardiopulmonary resuscitation | 11 (3.9%) | 7 (7.1%) | 4 (2.2%) | 0.038 | 4.8% | 3.0% | 0.47 |
| Abnormal troponin, % of checked[a] | 216 (82.1%) | 67 (76.1%) | 149 (85.1%) | 0.072 | 80.2% | 83.3% | 0.56 |
| Abnormal brain natriuretic peptide, % of checked[b] | 144 (71.6%) | 44 (80.0%) | 100 (68.5%) | 0.11 | 79.2% | 69.0% | 0.23 |
| Abnormal lactate, % of checked[c] | 92 (48.9%) | 41 (74.5%) | 51 (38.3%) | < 0.001 | 64.7% | 43.7% | 0.038 |
| Sequential Organ Failure Assessment[d], median (IQR) | 2 (1, 4) | 3 (1, 6) | 2 (1, 3) | 0.003 | 1.6 (0.5, 3.8) | 1.9 (1.0, 3.4) | 0.92 |
| Antiplatelet agent within 7 d before alteplase | 72 (25.4%) | 37 (37.8%) | 35 (18.8%) | < 0.001 | 26.8% | 25.1% | 0.78 |
| Anticoagulant within 7 d before alteplase | 228 (80.3%) | 81 (82.7%) | 147 (79.0%) | 0.47 | 80.5% | 80.0% | 0.94 |
| Trauma or invasive procedure within 30 d before | 40 (14.2%) | 17 (17.3%) | 23 (12.6%) | 0.27 | 17.2% | 16.0% | 0.84 |

IQR = interquartile range.

[a]Checked in 263 patients (88 full dose and 175 reduced dose).

[b]Checked in 201 patients (55 full dose and 146 reduced dose).

[c]Checked in 188 patients (55 full dose and 133 reduced dose).

[d]Available in 256 patients (80 full dose and 176 reduced dose).

# TABLE 2.
## Outcomes of Patients With Pulmonary Embolism Treated With Systemic Thrombolysis

| | Unweighted Cohort | | | | Weighted Cohort | | |
|---|---|---|---|---|---|---|---|
| | Total ($n = 284$) | Full Dose ($n = 98$) | Reduced Dose ($n = 186$) | $p$ | Full Dose ($n = 98$) | Reduced Dose ($n = 186$) | $p$ |
| SBP (before), mean (SD) | 103.8 (22.0) | 94.2 (22.2) | 108.8 (20.1) | < 0.001 | 99.6 (24.2) | 105.0 (25.1) | 0.089 |
| SBP (after), mean (SD) | 110.8 (23.0) | 100.8 (24.0) | 115.8 (20.8) | < 0.001 | 104.1 (22.7) | 112.5 (30.0) | 0.071 |
| Before vs. after, $p$ | < 0.001 | 0.004 | < 0.001 | | 0.059 | < 0.001 | |
| HR (before), mean (SD ) | 114.0 (22.0) | 119.8 (23.3) | 111.1 (20.8) | 0.001 | 117.4 (24.2) | 112.7 (27.0) | 0.17 |
| HR (after), mean (SD ) | 92.7 (23.2) | 100.3 (27.4) | 89.0 (19.9) | < 0.001 | 98.9 (28.3) | 89.5 (25.3) | 0.009 |
| Before vs. after, $p$ | < 0.001 | < 0.001 | < 0.001 | | < 0.001 | < 0.001 | |
| Shock index (before), mean (SD) | 1.17 (0.43) | 1.37 (0.52) | 1.07 (0.34) | < 0.001 | 1.27 (0.49) | 1.14 (0.49) | 0.049 |
| Shock index (after), mean (SD) | 0.89 (0.52) | 1.10 (0.80) | 0.79 (0.26) | < 0.001 | 1.02 (0.61) | 0.83 (0.32) | 0.006 |
| Before vs. after, $p$ | < 0.001 | < 0.001 | < 0.001 | | < 0.001 | < 0.001 | |
| RR (before), mean (SD) | 27.0 (7.3) | 29.9 (8.2) | 25.4 (6.4) | < 0.001 | 28.7 (9.3) | 26.1 (7.2) | 0.025 |
| RR (after), mean (SD) | 22.8 (6.4) | 25.7 (6.2) | 21.3 (6.1) | < 0.001 | 25.6 (7.2) | 21.9 (8.2) | 0.001 |
| Before vs. after, $p$ | < 0.001 | < 0.001 | < 0.001 | | 0.002 | < 0.001 | |
| Supplemental $O_2$ (before) | 220 (77.7%) | 78 (80.4%) | 142 (76.3%) | 0.43 | 76.7% | 78.3% | 0.81 |
| Supplemental $O_2$ (after) | 174 (63.7%) | 58 (63.0%) | 116 (64.1%) | 0.87 | 56.2% | 65.4% | 0.22 |
| Before vs. after, $p$ | < 0.001 | 0.005 | < 0.001 | | 0.002 | < 0.001 | |
| NIV, before | 35 (12.5%) | 18 (18.8%) | 17 (9.3%) | 0.023 | 13.4% | 12.1% | 0.77 |
| NIV, after | 19 (7.0%) | 11 (12.4%) | 8 (4.4%) | 0.017 | 9.0% | 6.5% | 0.50 |
| Before vs. after, $p$ | 0.003 | 0.052 | 0.021 | | 0.15 | 0.018 | |
| Mechanical ventilator (before) | 24 (8.5%) | 13 (13.5%) | 11 (5.9%) | 0.031 | 9.4% | 8.9% | 0.89 |
| Mechanical ventilator (after) | 22 (8.0%) | 11 (12.0%) | 11 (6.0%) | 0.086 | 8.8% | 8.2% | 0.87 |
| Before vs. after, $p$ | 0.32 | 0.32 | 0.56 | | 0.26 | 0.94 | |
| Vasopressor (before) | 47 (16.5%) | 27 (27.6%) | 20 (10.8%) | < 0.001 | 17.5% | 16.7% | 0.87 |
| Vasopressor (after) | 38 (13.8%) | 26 (27.7%) | 12 (6.6%) | < 0.001 | 18.1% | 10.7% | 0.14 |
| Before vs. after, $p$ | 0.30 | 0.74 | 0.11 | | 0.65 | 0.062 | |
| Catheter-directed intervention | 9 (3.%) | 2 (2.0%) | 7 (3.8%) | 0.43 | 1.9% | 4.5% | 0.31 |
| Surgical embolectomy | 1 (0.4%) | 1 (1.0%) | 0 (0.0%) | 0.17 | 0.5% | 0.0% | 0.32 |

(*Continued*)

## TABLE 2. (*Continued*)

### Outcomes of Patients With Pulmonary Embolism Treated With Systemic Thrombolysis

| | Unweighted Cohort | | | | Weighted Cohort | | |
|---|---|---|---|---|---|---|---|
| | Total (*n* = 284) | Full Dose (*n* = 98) | Reduced Dose (*n* = 186) | *p* | Full Dose (*n* = 98) | Reduced Dose (*n* = 186) | *p* |
| Hospital LOS (d), median (IQR) | 4.3 (2.9, 6.9) | 5.1 (3.3, 7.8) | 3.9 (2.8, 6.3) | 0.011 | 5.0 (3.1, 7.0) | 4.3 (2.9, 7.0) | 0.87 |
| ICU LOS (d), median (IQR) | 1.6 (1.0, 2.8) | 1.8 (1.1, 3.3) | 1.5 (1.0, 2.5) | 0.091 | 1.6 (0.9, 2.8) | 1.7 (1.0, 2.6) | 0.89 |
| Discharge destination | | | | 0.008 | | | 0.13 |
| Home | 214 (79.3%) | 61 (68.5%) | 153 (84.5%) | | 74.2% | 82.5% | |
| LTACH/SNF | 44 (16.3%) | 23 (25.8%) | 21 (11.6%) | | 22.9% | 12.5% | |
| Hospice/comfort care | 12 (4.4%) | 5 (5.6%) | 7 (3.9%) | | 2.9% | 5.0% | |
| Readmission | 26 (9.2%) | 13 (13.3%) | 13 (7.0%) | 0.081 | 12.0% | 6.6% | 0.18 |
| Pulmonary embolism-related mortality within 7 d | 11 (3.9%) | 6 (6.1%) | 5 (2.7%) | 0.15 | 4.0% | 4.2% | 0.93 |
| All-cause mortality within 7 d | 19 (6.7%) | 9 (9.2%) | 10 (5.4%) | 0.22 | 5.6% | 8.0% | 0.45 |
| All-cause mortality within 30 d | 24 (8.5%) | 14 (14.3%) | 10 (5.4%) | 0.010 | 8.6% | 8.0% | 0.86 |
| All-cause mortality within 1 yr | 44 (15.5%) | 21 (21.4%) | 23 (12.4%) | 0.045 | 14.2% | 17.3% | 0.50 |

HR = heart rate, beats per minute, IQR = interquartile range, LOS = length of stay, LTACH = long-term acute care hospital, NIV = noninvasive ventilation, RR = respiratory rate, respirations per minute, SBP = systolic blood pressure, mm Hg, SNF = skilled nursing facility.

# TABLE 3.
## Outcomes Among Patients With Massive and Submassive PE

| | Unweighted Cohort | | | | Weighted Cohort | | |
|---|---|---|---|---|---|---|---|
| Massive PE | Total ($n = 97$) | Full Dose ($n = 55$) | Reduced Dose ($n = 42$) | $p$ | Full Dose ($n = 55$) | Reduced Dose ($n = 42$) | $p$ |
| Hospital LOS (d), median (IQR) | 5.9 (3.4, 9.5) | 5.2 (3.0, 10.3) | 6.1 (3.6, 9.5) | 0.53 | 5.1 (3.1, 9.6) | 6.1 (3.5, 11.5) | 0.56 |
| ICU LOS (d) | | | | 0.39 | | | 0.52 |
| *n* | 80 | 42 | 38 | | 43.3 | 36.9 | |
| Median (IQR) | 2.0 (1.1, 3.4) | 1.9 (1.1, 4.6) | 2.0 (0.9, 2.8) | | 1.9 (1.1, 4.6) | 2.0 (1.0, 3.2) | |
| Discharge destination | | | | 0.23 | | | 0.58 |
| Missing | 13 | 9 | 4 | | 8.7 | 6.4 | |
| Home | 52 (61.9%) | 26 (56.5%) | 26 (68.4%) | | 56.0% | 64.1% | |
| LTACH/SNF | 23 (27.4%) | 16 (34.8%) | 7 (18.4%) | | 37.0% | 25.0% | |
| Hospice/comfort care | 9 (10.7%) | 4 (8.7%) | 5 (13.2%) | | 7.1% | 10.8% | |
| PE-related mortality within 7 d | 10 (10.3%) | 6 (10.9%) | 4 (9.5%) | 0.82 | 10.9% | 10.6% | 0.97 |
| All-cause mortality within 7 d | 17 (17.5%) | 9 (16.4%) | 8 (19.0%) | 0.73 | 14.8% | 22.5% | 0.38 |
| All-cause mortality within 30 d | 21 (21.6%) | 13 (23.6%) | 8 (19.0%) | 0.59 | 21.7% | 22.5% | 0.94 |
| All-cause mortality within 1 yr | 34 (35.1%) | 18 (32.7%) | 16 (38.1%) | 0.58 | 31.7% | 41.9% | 0.35 |
| Submassive PE | Total ($n = 184$) | Full Dose ($n = 43$) | Reduced Dose ($n = 141$) | $p$ | Full Dose ($n = 43$) | Reduced Dose ($n = 141$) | $p$ |
| Hospital LOS (d), median (IQR) | 3.9 (2.9, 5.9) | 5.0 (3.4, 7.2) | 3.6 (2.8, 5.6) | 0.006 | 5.0 (3.1, 6.2) | 3.8 (2.8, 5.6) | 0.90 |
| ICU LOS (d) | | | | 0.41 | | | 0.38 |
| *n* | 172 | 38 | 134 | | 36.5 | 134.6 | |
| Median (IQR) | 1.5 (1.0, 2.4) | 1.7 (0.9, 2.8) | 1.4 (1.0, 2.2) | | 1.2 (0.9, 2.2) | 1.5 (1.0, 2.2) | |
| Discharge destination | | | | 0.48 | | | 0.48 |
| Missing | 1 | 0 | 1 | | 0 | 0.8 | |
| Home | 159 (86.9%) | 35 (81.4%) | 124 (88.6%) | | 84.0% | 89.3% | |
| LTACH/SNF | 21 (11.5%) | 7 (16.3%) | 14 (10.0%) | | 15.1% | 8.6% | |
| Hospice/comfort care | 3 (1.6%) | 1 (2.3%) | 2 (1.4%) | | 0.9% | 2.1% | |
| PE-related mortality within 7 d | 1 (0.5%) | 0 (0.0%) | 1 (0.7%) | 0.58 | 0.0% | 0.6% | 0.61 |
| All-cause mortality within 7 d | 2 (1.1%) | 0 (0.0%) | 2 (1.4%) | 0.43 | 0.0% | 2.0% | 0.34 |
| All-cause mortality within 30 d | 3 (1.6%) | 1 (2.3%) | 2 (1.4%) | 0.68 | 0.9% | 2.0% | 0.62 |
| All-cause mortality within 1 yr | 10 (5.4%) | 3 (7.0%) | 7 (5.0%) | 0.61 | 2.8% | 5.2% | 0.52 |

IQR = interquartile range, LOS = length of stay, LTACH = long-term acute care hospital, PE = pulmonary embolism, SNF = skilled nursing facility.

### Complications

In the unweighted cohort, the overall rates of hemorrhagic complications were significantly lower in the reduced-dose group than in the full-dose group (13% vs. 24.5%, respectively, $p = 0.014$). The majority of hemorrhages were minor (10.8% in reduced-dose vs. 17.4% in full-dose, $p = 0.17$), whereas major extracranial hemorrhage occurred in 1.1% and 6.1%, $p = 0.022$ of cases, respectively. The differences persisted in the PS weighted cohort (1.3% in reduced-dose vs. 7.1% in full-dose for major, $p = 0.067$ and 12.8% in reduced-dose vs. 17.2% in full-dose, $p = 0.32$ for minor) but did not reach statistical significance (**Table 4**).

ICH occurred in one patient treated with the full-dose and two patients treated with reduced-dose regimen (1% and 1.1%, $p = 0.99$). In two cases, levels of heparin anticoagulation at the time of complication were significantly above therapeutic threshold. Both patients had a full recovery without neurologic deficits. In the third case, ICH occurred in an elderly patient with massive PE who received 100 mg of alteplase followed by heparin infusion; no coagulation labs were obtained.

Additional hemorrhage risk factors were identified in the majority of patients: 91.7% of them were systemically anticoagulated at the time of the complication development, with anticoagulation levels being in the supratherapeutic range in 37.5% of cases; 31.3% of patients underwent an invasive procedure close to the time of alteplase administration.

Hemorrhage occurred beyond the 24-hour post-alteplase window in 14 (29.2%) cases, and 7 of them were greater than 48 hours after alteplase completion.

A multivariable logistic regression model revealed that after adjusting for patient's age, weight, alteplase dose, and use of antiplatelet agents, invasive procedure performed within 30 days of thrombolysis was independently associated with hemorrhagic complications (**Supplemental Table 2**, http://links.lww.com/CCM/H473).

## DISCUSSION

Consistent with previous publications, our study demonstrated improvement in hemodynamic and respiratory parameters following systemic thrombolysis (15, 25–27). Significant improvements were noted in both, reduced- and full-dose alteplase groups at the 8-hour post-alteplase interval, confirming the previously demonstrated rapid onset of positive effects of systemic thrombolysis (14). There were no significant differences between groups in discharge destination, ICU and hospital LOS, or readmission rates. Mortality rates in our study were consistent with the previously published data and were similar in the full- and reduced-dose groups, with patients with massive PE accounting for the majority of deaths in our cohort

## TABLE 4.
### Hemorrhagic Complications

| | | Unweighted Cohort | | | Weighted Cohort | | |
|---|---|---|---|---|---|---|---|
| | Total ($n = 284$) | Full Dose ($n = 98$) | Reduced Dose ($n = 186$) | $p$ | Full Dose ($n = 98$) (%) | Reduced Dose ($n = 186$) (%) | $p$ |
| Hemorrhage, any | 48 (17.0%) | 24 (24.5%) | 24 (13.0%) | 0.014 | 24.7 | 15.4 | 0.12 |
| Minor | 37 (13.1%) | 17 (17.4%) | 20 (10.8%) | 0.17 | 17.2 | 12.8 | 0.32 |
| Major extracranial | 8 (2.8%) | 6 (6.1%) | 2 (1.1%) | 0.022 | 7.1 | 1.3 | 0.067 |
| Intracranial | 3 (1.1%) | 1 (1.0%) | 2 (1.1%) | 0.99 | 0.5 | 1.5 | 0.46 |
| Among those with any hemorrhage | | | | | | | |
| Invasive procedure | 15 (31.3%) | 10 (41.7%) | 5 (20.8%) | 0.12 | 39.9 | 16.1 | 0.053 |
| Systemic anticoagulation | 44 (91.7%) | 22 (91.7%) | 22 (91.7%) | 0.99 | 94.9 | 86.8 | 0.32 |
| Supratherapeutic anticoagulation[a] | 18 (37.5%) | 8 (33.3%) | 10 (41.7%) | 0.55 | 34.6 | 45.6 | 0.42 |

[a]Supratherapeutic anticoagulation = activated partial thromboplastin time > 2.5 times of control value or heparin activity > 0.7 units/mL.

(28–30). No significant differences between full- and reduced-dose regimens were detected when massive and submassive PE subgroups were analyzed separately. Although significant improvements in echocardiographic parameters with both alteplase dose regimens were in line with previous publications, the interpretation is limited by limitations in the data availability (15, 27). Overall, the study results suggest similar effectiveness of the full- and reduced-dose alteplase regimens in patients with PE.

The reported rates of hemorrhagic complications in patients with PE treated with systemic thrombolysis are highly variable (12, 13, 31–33). The majority of hemorrhages in our cohort were minor. The rate of major hemorrhage was lower in the reduced-dose as compared with the full-dose group, with the low number of events likely responsible for the differences not reaching statistical significance after the PS weighting. These findings are consistent with the earlier reports demonstrating similar benefits and lower bleeding rates in patients treated with the reduced-dose alteplase regimen (17, 34, 35). The dose effect is further supported by the association of a higher alteplase dose with postthrombolytic coagulopathy (36, 37). Reports of successful use of even a lower dose (25 mg) alteplase in patients with PE suggest the need for additional studies to determine the optimal systemic thrombolysis dose regimen (38, 39).

Additional factors likely contributed to the development of complications in many cases. Almost all hemorrhages occurred in the setting of full systemic anticoagulation, with supratherapeutic anticoagulation levels noted in over a third of the cases. Supratherapeutic anticoagulation levels and coagulopathy were noted in two of the three ICH cases, whereas the laboratory values were not available in the third case. About a quarter of the hemorrhages were related to invasive procedures such as venous or arterial vascular access or recent surgery, and a substantial number occurred more than 24 hours after the alteplase administration. These findings demonstrate the complexity of the circumstances where complications occur, as systemic anticoagulation alone can be associated with a major hemorrhage in 2–7% of cases (12, 13, 40, 41).

Our study demonstrates clinicians commonly use the reduced-dose alteplase regimen, especially in non-massive PE settings. Despite multiple known risk factors, it is difficult to predict individual risk of hemorrhage (8, 32, 42). Although not a substitute for a randomized controlled trial, PS weighting used in this study allowed for comparison of outcomes in the reduced- and full-dose thrombolysis cohorts. The strength of this study is its reflection of a real-world multicenter experience of thrombolysis utilization and outcomes in patients with PE over a long time period. Individual chart review allowed for a better understanding of the circumstances and causes of hemorrhagic complications.

Limitations include the possibility of unmeasured confounders and bias related to the retrospective observational study design and data collection that may explain our findings. Other limitations include data availability limitations due to the electronic health records evolution that could have missed pertinent information, and limited availability of the echocardiographic data. While stringent criteria were used for the manual data collection where data extraction was not sufficient, residual confounding related to this process is possible.

Although it is challenging to conduct clinical trials on thrombolysis in acute PE setting, exemplified by a fairly limited number of cases in this multicenter analysis encompassing a 9-year interval, there is need to further evaluate the comparative effectiveness, safety, and costs of the reduced- and full-dose alteplase regimens and to compare them to the catheter-based interventions and third-generation thrombolytic agents that have longer half-life, higher fibrin specificity, and can be administered in a single IV bolus (43–46). Individualized approach, with treatment algorithms taking into account patient presentation, comorbid conditions, response to the initial treatment, and risks and benefits of reperfusion therapy may result in best outcomes.

## CONCLUSIONS

In a retrospective, PS-weighted observational study of patients with PE receiving reperfusion therapy, reduced-dose alteplase results in outcomes similar to the full-dose regimen but is associated with a lower risk of bleeding. Cautious heparin titration strategies to avoid excessive anticoagulation levels as well as avoidance of invasive procedures, when possible, may further reduce complications.

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