Thrombolytic Therapy and Mortality in Patients With Acute Pulmonary Embolism

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Background: In the management of acute pulmonary embolism, the prevalence of thrombolytic therapy is uncertain, and its benefits compared with standard anticoagulation remain a subject of debate.

Methods: This analysis included 15,116 patient discharges with a primary diagnosis of pulmonary embolism from 186 acute care hospitals in Pennsylvania (January 2000 to November 2002). We compared propensity score–adjusted mortality between patients who received thrombolysis and those who did not, using logistic regression to model mortality within 30 days of presentation and Poisson regression to model in-hospital mortality.

Results: Of the 15,116 patient discharges, only 356 (2.4%) received thrombolytic therapy. The overall 30-day mortality rate for patients who received thrombolytic therapy was 17.4% compared with 8.6% for those who did not. The corresponding in-hospital mortality rates were 19.6 and 8.3, respectively, per 1000 person-days. However, mortality risk associated with thrombolysis varied with the propensity to receive thrombolysis: the odds ratios of 30-day mortality were 2.8 ($P=.007$), 3.9 ($P<.001$), 1.8 ($P=.09$), 1.0 ($P=.98$), and 0.7 ($P=.30$) for patients in the lowest to the highest quintiles of the propensity score distribution who received thrombolysis. A similar pattern was observed in the risk ratios for in-hospital death.

Conclusions: In this large sample of patients hospitalized for acute pulmonary embolism, thrombolytic therapy was used infrequently. Risk of in-hospital and 30-day mortality appears to be elevated for patients who were unlikely candidates for this therapy based on characteristics at presentation, but not for patients with a relatively high predicted probability of receiving thrombolysis.

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The standard treatment for acute pulmonary embolism (PE) consists of initial unfractionated or low-molecular-weight heparins to stabilize the clot and reduce clot progression, followed by oral anticoagulation therapy for 3 months or longer.1-3 Thrombolytic therapy provides the opportunity to degrade clot bound to the fibrinogen, resulting in faster clot resolution with the potential to improve pulmonary blood flow and cardiopulmonary status.4 However, the indications for thrombolytic therapy in acute PE and its benefits over and above that of standard anticoagulation remain a subject of considerable debate.5-7 The most commonly recognized indication for thrombolytic therapy in the management of acute PE is cardiopulmonary compromise as signaled by systolic hypotension, cardiogenic shock, or right ventricular dysfunction.5,8 For patients with uncomplicated PE, the Seventh American College of Chest Physicians (ACCP) guideline consensus recommends that clinicians not use systemic thrombolytic therapy (grade 1A).9

See Invited Commentary at the end of this article

The clinical benefits of thrombolytic therapy in the management of acute PE have been evaluated in several small randomized controlled studies10-12 and several larger nonrandomized studies.13-15 These studies have shown no consistent association between the use of thrombolytic therapy and mortality in patients with PE, regardless of patients’ cardiopulmonary status. The most recent randomized controlled trial reported that, compared with standard anticoagulation therapy, primary thrombolytic therapy reduced the combined end points of mortality and...
treatment escalation. However, mortality alone did not differ between those who received thrombolytic therapy and those who received standard anticoagulation. Further fueling the debate, a cost-effectiveness analysis of thrombolytic therapy in acute PE concluded that routine use of this treatment in hemodynamically stable patients with submassive acute PE is neither effective nor cost-effective compared with standard anticoagulation.

It is unclear how this inconsistent evidence regarding indications for and benefits of thrombolytic therapy in acute PE is operationalized into clinical practice outside of research-intensive academic health care settings or the highly specialized clinical care settings contributing to research registries. To address this knowledge gap, we analyzed a large statewide database involving both community and academic hospitals to assess the prevalence of thrombolytic therapy and its association with 30-day and in-hospital mortality among 15,116 cases of acute PE.

DATA COLLECTION

Our study cohort was identified using the Pennsylvania Health Care Cost Containment Council (PHC4) Database, which includes demographic data from all patient discharges from nongovernmental (ie, non–Veterans Administration) acute care hospitals in Pennsylvania. The cohort comprised all patients 18 years or older who were discharged with a primary diagnosis of PE from January 2000 to November 2002 based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 415.1, 415.11, 415.19, and 673.20 to 673.24. We also included patients who had a secondary diagnosis of PE and one of the following primary diagnoses that represent likely complications or treatments for PE: respiratory failure (code 518.81), cardiogenic shock (code 785.51), cardiac arrest (code 427.3), secondary pulmonary hypertension (code 416.8), syncope (code 780.2), thrombolysis (code 99.10), and intubation or mechanical ventilation (codes 96.04, 96.05, and 96.70 to 96.72). Patients with recurrent PE may have a higher mortality than patients with a first episode; therefore, we included all episodes of PE within the study period. We excluded discharges with missing patient identifiers or unknown mortality status. The institutional review board at the University of Pittsburgh, Pittsburgh, Pennsylvania, approved this study.

BASELINE DATA AND STUDY OUTCOMES

Patient baseline clinical variables were obtained by linking study patients to the Atlas Database (MediQual, Marlborough, Massachusetts), which includes detailed clinical findings at presentation for all inpatients treated at nongovernmental acute care hospitals in Pennsylvania. These variables include insurance status, comorbid conditions, and the physical examination findings given in Table 1. During a patient’s admission process, patient sex and race were either self-reported or determined by administrative staff.

Our study outcomes were unadjusted and adjusted for propensity score all-cause mortality within 30 days of presentation and in-hospital mortality. We obtained out-of-hospital mortality data by linking study patients to the National Death Index.

STATISTICAL METHODS

We used logistic regression to conduct our unadjusted (univariate) comparisons of baseline clinical and demographic characteristics between patients who received thrombolytic therapy and those who did not. We used a robust variance estimator clustered at the hospital level and a 2-tailed P value of <.05 to define statistical significance throughout.

Thrombolytic therapy was not randomly allocated, so patients who received thrombolysis could differ systematically from patients who did not with respect to baseline characteristics, clinical examination findings, and comorbid conditions. When these characteristics are related to mortality outcomes, a direct comparison between the 2 treatment groups is likely to be biased. To account for this potential bias, we used a propensity score adjustment to compare treatment effects for patients with similar predicted probabilities of receiving thrombolytic therapy. The goal of propensity score adjustment is to improve covariate balance across the 2 treatment arms. In the absence of unmeasured confounding, propensity score adjustment mimics an unbalanced random assignment of treatments within subgroups of patients with similar predicted probabilities of receiving the treatment.

We used logistic regression to estimate the propensity score. We modeled the receipt of thrombolytic therapy using baseline demographic and clinical variables that potentially are related to the receipt of thrombolytic therapy or clinically likely to influence a decision regarding thrombolytic therapy. These variables (listed in Table 1) include predictors of disease severity based on a validated prognostic model for PE, the Pulmonary Embolism Severity Index (PESI). This prognostic model consists of 11 routinely available predictors of mortality from PE: age, male sex, 3 comorbid conditions (cancer, chronic lung disease, and heart failure) and 6 clinical factors (pulse ≥110/min, systolic blood pressure <100 mm Hg, respiratory rate ≥30/min, body temperature <36°C, altered mental status, and oxygen saturation <90%). We included the component variables rather than the PESI summary score in the propensity score model, as well as the remaining variables in Table 1. We matched the propensity scores of patients who did not receive thrombolysis to the quintiles of the propensity score distribution of patients who did. This matching was done to balance the relatively small number of patients who received thrombolysis across the propensity score strata used in the primary outcome comparisons.

To assess covariate balance, we estimated the unadjusted and propensity score–adjusted odds ratios (ORs) of receiving thrombolysis by fitting separate logistic regression models with each individual covariate as the primary independent variable. The adjusted models included dummy variables for the propensity score quintiles. We assessed whether the propensity score–adjusted ORs were attenuated and less statistically significant than the corresponding unadjusted estimates.

We used logistic regression to model the association between 30-day mortality and thrombolytic therapy status and Poisson regression to model the association between in-hospital mortality and thrombolytic therapy status (to account for person-time at risk). In both types of models, a robust variance estimator clustered at the hospital level accounted for intrasite correlation. The unadjusted analyses included thrombolysis therapy status as the only predictor; the adjusted models also included dummy variables for quintiles of the propensity score. We tested the interaction of thrombolysis and the categorized propensity score to assess whether the magnitude of the association varied by propensity score quintile. All statistical analyses were performed using Stata version 10.0 (StataCorp, College Station, Texas).
These analyses were repeated for the subgroup of patients with systolic blood pressure lower than 90 mm Hg (ie, hemodynamically unstable patients), who traditionally are thought to benefit from thrombolytic therapy in the setting of acute PE. For completeness, we repeated these analyses for the remaining subgroup of hemodynamically stable patients. We also repeated the primary analyses excluding patients who had either a stroke or myocardial infarction (20 thrombolysis patients and 295 nonthrombolysis patients) because stroke and myocardial infarction are the only other major indications for systemic thrombolysis.

### RESULTS

Of 17,733 cases of PE identified on the basis of ICD-9-CM codes for PE, 2,202 were excluded because either they had only a secondary ICD-9-CM code for PE (n=323), were transferred from another hospital (n=767), were transferred to another hospital (n=265), had no key clinical find-
ings (n = 777), or had an unknown mortality status (n = 70). Because major bleeding is a clear contraindication to thrombolytic therapy, we also excluded 415 patients who had a diagnosis of major bleeding (defined as intracerebral hemorrhage, other unspecified intracranial hemorrhage, or bleeding that required transfusion of red blood cells) and did not receive any thrombolytic therapy.

BASELINE PATIENT CHARACTERISTICS

In the analytic sample (N = 15,116), 80.9% of patients were white, 10.8% were black, and 8.4% were of other or unknown race. Thrombolytic therapy was received by 284 white patients (2.3%), 45 black patients (2.8%), and 27 patients of other/unknown race (2.1%). There were only 3 cases of surgical embolectomy.

Patients who received thrombolytic therapy were more likely to be younger (P < .001), male (P = .01), and covered by private insurance (P < .001) (Table 1). Patients who received thrombolytic therapy were less likely to have diagnoses of lung disease, heart failure, and/or cerebrovascular disease and more likely to have diagnoses of ischemic heart disease, pulmonary vascular disease, and/or syncope (P < .02 for each).

On physical examination at the time of presentation to the hospital, patients who received thrombolytic therapy were more likely than those who did not to register a higher pulse rate (>110/min), lower systolic blood pressure (<100 mm Hg), higher respiration rate (>30/min), hypothermia (temperature <36°C), hypoxemia (arterial oxygen saturation rate <90%), renal insufficiency (creatinine level >1.5 mg/dL [to convert to micromoles per liter, multiply by 88.4]), and/or acidosis (arterial pH <7.25). They were also more likely to have an elevated troponin level (≥0.1 ng/mL [to convert to micrograms per liter, multiply by 1.0]), abnormal PCO₂ (<25 or >55 mm Hg), higher mean or systolic pulmonary arterial pressure (>40 mm Hg), and/or enlarged heart (cardiomegaly) on chest radiography. These differences are summarized in Table 1 (P < .01 for each).

THE PROPENSITY SCORE ADJUSTMENT

The propensity score model included all of the variables listed in Table 1 except for the summary variable denoting PESI risk class. Propensity score adjustment eliminated the 23 statistically significant unadjusted differences (given in Table 1) between those who did and did not receive thrombolysis and attenuated the corresponding ORs. Among those who did not receive thrombolysis, 56.7% were in the lowest propensity score quintile, 21.9% were in the second, 14.7% were in the third, 4.6% in the fourth, and 2.1% were in the highest quintile; relatively few patients who did not receive thrombolysis “looked like” those who did with respect to their propensity scores.

THE RELATIONSHIP BETWEEN MORTALITY AND RECEIPT OF THROMBOLYTIC THERAPY

Table 2 summarizes 30-day mortality by observed thrombolysis status, both overall and by quintile of the propensity score distribution for all 15,116 hospitalizations. The unadjusted overall 30-day mortality rate for patients who did receive thrombolytic therapy was 17.4%, compared with 8.6% for those who did not receive this treatment (OR, 2.2 [95% confidence interval {CI}, 1.7-3.0]; P < .001). However, the logistic regression analysis indicated significant heterogeneity in the stratum-specific ORs (P = .001); except for the lowest propensity score category, the ORs generally decrease with increasing propensity to receive thrombolysis. The category-specific ORs and pointwise 95% CIs are shown by the median propensity in the Figure, A. These ORs were significantly elevated for those in the lowest 2 propensity score quintiles who received thrombolysis (OR, 2.8 [95% CI, 1.3-5.9], and OR, 3.9 [95% CI 2.2-7.1], respectively; P < .01 for each). In Table 2, the ORs were nonsignificantly elevated for those with propensity between 0.027 and 0.057 (OR, 1.8 [95% CI, 0.9-3.6]; P = .09) and nonsignificantly reduced for the highest 2 categories (OR, 1.0 [95% CI, 0.5-2.0], and OR, 0.7 [95% CI, 0.3-1.4]; P > .29 for each).

For those who received and did not receive thrombolysis, the overall in-hospital mortality rates were 19.6 and 8.3 per 1000 person-days, respectively (Table 3), which corresponded to an overall risk ratio of 2.3 (95% CI, 1.8-3.1) (P < .001). Among patients who received thrombolysis, 93.5% of the deaths within 30 days occurred in the hospital, whereas among patients who did not receive thrombolysis, 63.2% of these deaths oc-
curred in the hospital. The risk ratios varied significantly over the categories of the propensity score \( P = .002 \), and except for the lowest quintile, the risk ratios decreased with increasing propensity score. The pattern of the category-specific risk ratios and pointwise 95% CIs in the Figure, B, is similar to that of the ORs for 30-day mortality.

Almost one-third of the deaths among patients who received thrombolysis and about 15% of deaths among patients who did not receive thrombolysis occurred in the small subgroup (5.3%) of hemodynamically unstable patients (Table 4). Both the ORs in Table 4 and the risk ratios in Table 5 followed the general pattern observed for all patients, i.e., elevated risk for the lowest 3 propensity score categories, followed by equivocal or somewhat reduced risk for the fourth and fifth categories. The hemodynamically stable patients comprised almost 95% of the study population; results for this subgroup paralleled those of the entire study population (Table 6 and Table 7) except that the risk ratio for the middle propensity score quintile was only 1.02 for this subgroup. Results were similar when we excluded the 315 patients with myocardial infarction and/or stroke.

![Figure](https://example.com/figure.png)

**Figure.** Risk of mortality by quintile of the propensity score, plotted at the median value within each propensity score category. The figure shows the odds ratios of 30-day mortality (A) and in-hospital mortality (B) for those who received thrombolysis relative to those who did not, with corresponding 95% confidence intervals.

### Table 3. In-Hospital Mortality Within 30 Days per 1000 Person-Days by Thrombolysis Status and Quintile of the Predicted Probability of Receiving Thrombolysis for All Hospitalizations

<table>
<thead>
<tr>
<th>Predicted Probability of Thrombolysis*</th>
<th>No Thrombolysis</th>
<th>Yes Thrombolysis</th>
<th>Risk Ratio, Risk Ratio, No Thrombolysis/Yes Thrombolysis</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.016</td>
<td>381 65 132.6 6.9</td>
<td>14 559.0 25.0</td>
<td>3.6 &lt;.001</td>
<td></td>
</tr>
<tr>
<td>0.016-0.027</td>
<td>122 20 342.3 6.0</td>
<td>14 623.0 22.5</td>
<td>3.7 &lt;.001</td>
<td></td>
</tr>
<tr>
<td>0.028-0.057</td>
<td>179 14 202.4 12.6</td>
<td>11 650.0 16.9</td>
<td>1.3 .45</td>
<td></td>
</tr>
<tr>
<td>0.058-0.109</td>
<td>75 4543.2 16.5</td>
<td>9 586.1 15.4</td>
<td>0.9 .85</td>
<td></td>
</tr>
<tr>
<td>&gt;0.109</td>
<td>47 2119.2 22.2</td>
<td>10 541.1 18.5</td>
<td>0.8 .63</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>904 96 339.6 8.3</td>
<td>58 2959.2 19.8</td>
<td>2.3 &lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

*Quintiles are based on the propensity score distribution of patients who actually received thrombolysis.

**Abbreviations:** Th(+) thrombolysis received; Th(−) thrombolysis not received.

\( ^{*} \)Mortality of Th(+)mortality of Th(−).

### MAJOR BLEEDING AND THROMBOLYTIC THERAPY

Among the 356 patients who received thrombolytic therapy, 19 patients (5.3%) had had major bleeding, of whom 10 died. Among those who did not receive thrombolytic therapy, 415 had major bleeding (3.5%), of whom 104 died.

### COMMENT

In this large, statewide sample of patients hospitalized for acute PE, we found that receipt of thrombolytic therapy was associated with a significantly higher risk of death, both in-hospital and in the 30 days following admission, among patients with a low predicted probability of receiving thrombolysis based on characteristics at presentation. This may represent patients whose clinical condition deteriorates after admission. However, among the small subgroup with a relatively high predicted probability of receiving thrombolysis (the 7.5% with propensity scores >0.057), treatment with thrombolysis does
not appear to be associated with increased risk. The small
subgroup of patients with PE along with systolic hypo-
tension exhibited a similar pattern of risk.

The following 3 thrombolytic agents have been ap-
proved by the Food and Drug Administration (FDA) for
the management of acute PE in the United States: strep-
tokinase, urokinase, and tissue plasminogen activator.
The first 2 were FDA approved in 1977 and 1978, respec-
tively, and the last one in 1990. Although earlier studies
have shown that thrombolysis is better than anticoagula-

Table 4. Thirty-Day Mortality by Thrombolysis Status and Quintile of the Predicted Probability
of Receiving Thrombolysis for Patients With Hypotensiona

<table>
<thead>
<tr>
<th>Predicted Probability of Thrombolysisb</th>
<th>Thrombolysis Received</th>
<th>Thrombolysis Not Received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No, Mortality,</td>
<td>Yes, Mortality,</td>
</tr>
<tr>
<td></td>
<td>No./Total No. (%)</td>
<td>No./Total No. (%)</td>
</tr>
<tr>
<td>≤0.016</td>
<td>33/116 (28.5)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>0.016-0.027</td>
<td>27/122 (22.1)</td>
<td>2/3 (66.7)</td>
</tr>
<tr>
<td>0.028-0.057</td>
<td>61/244 (25.0)</td>
<td>5/9 (55.6)</td>
</tr>
<tr>
<td>0.058-0.109</td>
<td>36/140 (25.7)</td>
<td>5/16 (27.8)</td>
</tr>
<tr>
<td>&gt;0.109</td>
<td>37/124 (29.8)</td>
<td>6/26 (23.1)</td>
</tr>
<tr>
<td>Overall</td>
<td>194/746 (26.0)</td>
<td>19/57 (33.3)</td>
</tr>
</tbody>
</table>

Abbreviations: Th(+), thrombolysis received; Th(−), thrombolysis not received.
a Hypotension is defined as systolic blood pressure lower than 90 mm Hg.
b Quintiles are based on the propensity score distribution of patients who actually received thrombolysis.
c The first 2 quintiles were combined owing to the small number of patients with thrombolysis.

Table 5. In-Hospital Mortality Within 30 Days per 1000 Person-Days by Thrombolysis Status
and Quintile of the Predicted Probability of Receiving Thrombolysis for Patients With Hypotensiona

<table>
<thead>
<tr>
<th>Predicted Probability of Thrombolysisb</th>
<th>Thrombolysis Received</th>
<th>Thrombolysis Not Received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>Days at Risk</td>
</tr>
<tr>
<td>≤0.016</td>
<td>25</td>
<td>861.0</td>
</tr>
<tr>
<td>0.016-0.027</td>
<td>20</td>
<td>934.0</td>
</tr>
<tr>
<td>0.028-0.057</td>
<td>49</td>
<td>1754.1</td>
</tr>
<tr>
<td>0.058-0.109</td>
<td>25</td>
<td>990.1</td>
</tr>
<tr>
<td>&gt;0.109</td>
<td>28</td>
<td>823.2</td>
</tr>
<tr>
<td>Overall</td>
<td>147</td>
<td>5362.4</td>
</tr>
</tbody>
</table>

Abbreviations: Th(+), thrombolysis received; Th(−), thrombolysis not received.
a Hypotension is defined as systolic blood pressure lower than 90 mm Hg.
b Quintiles are based on the propensity score distribution of patients who actually received thrombolysis.
c Mortality of Th(+)/mortality of Th(−).
d The first 2 quintiles were combined owing to the small number of patients with thrombolysis.

Table 6. Thirty-Day Mortality by Thrombolysis Status and Quintile of the Predicted Probability
of Receiving Thrombolysis for Patients With a Systolic Blood Pressure of 90 mm Hg or Higher

<table>
<thead>
<tr>
<th>Predicted Probability of Thrombolysisb</th>
<th>Thrombolysis Received</th>
<th>Thrombolysis Not Received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No, Mortality,</td>
<td>Yes, Mortality,</td>
</tr>
<tr>
<td></td>
<td>No./Total No. (%)</td>
<td>No./Total No. (%)</td>
</tr>
<tr>
<td>≤0.016</td>
<td>634/8249 (7.7)</td>
<td>13/71 (18.3)</td>
</tr>
<tr>
<td>0.016-0.027</td>
<td>179/3110 (5.8)</td>
<td>13/68 (19.1)</td>
</tr>
<tr>
<td>0.028-0.057</td>
<td>182/1926 (9.5)</td>
<td>8/61 (13.1)</td>
</tr>
<tr>
<td>0.058-0.109</td>
<td>61/543 (11.2)</td>
<td>5/53 (9.4)</td>
</tr>
<tr>
<td>&gt;0.109</td>
<td>23/186 (12.4)</td>
<td>4/46 (8.7)</td>
</tr>
<tr>
<td>Overall</td>
<td>1079/14 014 (7.7)</td>
<td>43/299 (14.4)</td>
</tr>
</tbody>
</table>

Abbreviations: Th(+), thrombolysis received; Th(−), thrombolysis not received.
b Quintiles are based on the propensity score distribution of patients who actually received thrombolysis.
tion alone in early resolution of pulmonary artery blood clots and normalizing pulmonary artery and heart hemodynamics,\textsuperscript{21} this evidence has not been associated with increased uptake of thrombolytic therapy in routine clinical practice.\textsuperscript{2,22} This is partly attributable to the considerable hesitation among clinicians regarding the optimum use of thrombolytic therapy in acute PE management owing to concerns about the lack of a clear consensus on indications, fear of bleeding complications, and inconsistent evidence demonstrating solid long-term benefit of thrombolytic therapy over anticoagulation.

Our finding of a significant association between mortality and thrombolytic therapy in patients with PE with a relatively low predicted probability of receiving thrombolysis is consistent with the ACCP guideline recommendations against the use of thrombolytic therapy in hemodynamically uncomplicated patients with PE.\textsuperscript{8} Our results do not challenge the conventional thinking that massive PE with resultant hemodynamic instability (ie, cardiogenic shock) is a reasonable indication for thrombolytic therapy. After all, massive PE is associated with a significant (18%) risk of death,\textsuperscript{23} and the risk is even higher when accompanied by cardiogenic shock (30%).\textsuperscript{9,23} Recent studies, however, have suggested broadening the selection criteria for thrombolytic therapy in acute PE. For example, a 1993 study by Goldhaber et al\textsuperscript{11} was one of the first to apply echocardiographic indicators of right ventricular dysfunction in the evaluation of PE severity and potential benefits of thrombolytic use. Since that study, others have confirmed the relationship between right ventricular dysfunction in acute PE and higher mortality.\textsuperscript{13,26,27} Furthermore, the most recent and largest prospective randomized clinical trial of thrombolysis in acute PE, the Management Strategies and Prognosis of Pulmonary Embolism-3 Trial (MAPPET-3), reported that thrombolytic therapy improves the clinical course of hemodynamic instability.

Third, we have no long-term data on mortality, recurrent PE, or the occurrence of pulmonary hypertension, so we were unable to assess relationships between thrombolytic therapy and long-term outcomes after acute PE. Fourth, although the only known major adverse effect of thrombolysis is bleeding, most of the mortality in the thrombolysis group is not attributable to bleeding; this suggests low predicted probability of receiving thrombolysis contrast with previous reports of no higher mortality risk from thrombolytic therapy in acute PE management.\textsuperscript{15} A possible explanation is that our sample included patients for whom thrombolytic therapy was potentially harmful and should not have been used such as in clinically and hemodynamically stable patients with right ventricular dysfunction only.\textsuperscript{29} A potential reason for caution in the use of thrombolytic therapy in acute PE even in the setting of hemodynamic instability relates to the concerns about bleeding as a complication of therapy. A meta-analysis of 14 clinical trials involving 559 patients who received thrombolytic therapy (alteplase) reported a rate of intracerebral hemorrhage of 2.1%.\textsuperscript{4} Others have reported fatal bleeding rates around 2.2%.\textsuperscript{30} Major bleeding, defined as a drop in hemoglobin level of 2 g/dL (to convert to grams per liter, multiply by 10), a 2-unit transfusion of red blood cells, or retroperitoneal bleeding requiring intervention, occurred in 22% of patients who received thrombolysis for acute PE.\textsuperscript{14}

In contrast to these studies, bleeding rates were much smaller in our patient population.

There are important limitations to our study. First, although these data reflect the use of thrombolytic therapy in acute PE management in routine clinical practice in the state of Pennsylvania, other regions may differ. Second, our data do not include information on right ventricular function following acute PE or other potentially important prognostic factors after presentation. Such information would have been helpful to assess how hospitals have adopted some of the emerging, although not consistently accepted, indications of thrombolytic therapy in acute PE and whether changes in patients’ clinical condition after presentation account for the apparently elevated risk among patients with a low predicted probability of receiving thrombolysis. Third, we have no long-term data on mortality, recurrent PE, or the occurrence of pulmonary hypertension, so we were unable to assess relationships between thrombolytic therapy and long-term outcomes after acute PE. Fourth, although the only known major adverse effect of thrombolysis is bleeding, most of the mortality in the thrombolysis group is not attributable to bleeding; this suggests...
that thrombolytic therapy may not have been a direct cause of death for these patients. Unfortunately, our data do not allow us to identify the exact cause of death. Fifth, the relatively small number of patients who received thrombolyis, even in this large data set, limited our statistical analyses. Finally, although we have accounted for all relevant potential confounding variables available to us in our propensity score model, the possibility of residual confounding remains.

In conclusion, in this large sample of patients hospitalized with acute PE, thrombolytic therapy is used infrequently and is associated with a higher risk of both 30-day and in-hospital mortality in the large subgroup of patients with a relatively low predicted probability of receiving thrombolyis based on characteristics at presentation. Major bleeding was an uncommon complication of thrombolytic therapy. Clinical studies with more longitudinal prognostic information are needed to better explain the uptake, risks, and benefits of thrombolytic therapy in the management of acute PE in routine clinical practice.

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