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# Systemic thrombolysis increases hemorrhagic stroke risk without survival benefit compared with catheter-directed intervention for the treatment of acute pulmonary embolism

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## ABSTRACT

**Background:** Systemic thrombolysis (ST) and catheter-directed intervention (CDI) are both used in the treatment of acute pulmonary embolism (PE), but the comparative outcomes of these two therapies remain unclear. The objective of this study was to compare short-term mortality and safety outcomes between the two treatments using a large national database.

**Methods:** Patients presenting with acute PE were identified in the National Inpatient Sample (NIS) from 2009 to 2012. Comorbidities, clinical characteristics, and invasive procedures were identified using International Classification of Diseases, Ninth Revision (ICD) codes and the Elixhauser comorbidity index. To adjust for anticipated baseline differences between the two treatment groups, propensity score matching was used to create a matched ST cohort with clinical and comorbid characteristics similar to those of the CDI cohort. Subgroups of patients with and without hemodynamic shock were analyzed separately. Primary outcomes were in-hospital mortality, overall bleeding risk, and hemorrhagic stroke risk.

**Results:** Of 263,955 subjects with acute PE, 1.63% (n = 4272) received ST and 0.55% (n = 1455) received CDI. ST subjects were older, had more chronic comorbidities, and had higher rates of respiratory failure (ST, 27.9% [n = 1192]; CDI, 21.2% [n = 308]; $P < .001$) and shock (ST, 18.2% [n = 779]; CDI, 12% [n = 174]; $P < .001$). CDI subjects had higher rates of concurrent deep venous thrombosis (ST, 35.8% [n = 1530]; CDI, 45.9% [n = 668]; $P < .001$) and vena cava filter placement (ST, 31.1% [n = 1328]; CDI, 57% [n = 830]; $P < .001$). In the unmatched cohort, ST subjects had higher in-hospital mortality (ST, 16.7% [n = 714]; CDI, 9.4% [n = 136]; $P < .001$) and hemorrhagic stroke rates (ST, 2.2% [n = 96]; CDI, 1.4% [n = 20]; $P = .041$). After propensity matching, 1430 patients remained in each cohort; baseline characteristics of the matched cohorts did not differ significantly using standardized difference comparisons. Analysis of the matched cohorts did not demonstrate a significant effect of CDI on in-hospital mortality or overall bleeding risk but did show a significant protective effect against hemorrhagic stroke compared with ST (odds ratio, 0.47; 95% confidence interval, 0.27-0.82; $P = .01$). Subgroup analysis showed decreased odds of hemorrhagic stroke for CDI in the nonshock subgroup and increased procedural bleeding for CDI but no difference in hemorrhagic stroke risk in the shock subgroup.

**Conclusions:** ST for acute PE may not improve in-hospital mortality compared with CDI but increases the overall risk of hemorrhagic stroke compared with CDI. Further prospective studies should examine the comparative effectiveness and safety of these two treatments. (J Vasc Surg: Venous and Lym Dis 2016;■:1-6.)

Acute pulmonary embolism (PE) is a morbid condition with a wide severity spectrum, ranging from asymptomatic incidentally detected emboli to large PE causing hemodynamic instability and even death. Acute PE is classified into risk categories based on the presence of hemodynamic shock (high-risk or massive PE) or absence of shock but with evidence of myocardial necrosis or right-sided heart strain (intermediate-risk or submassive PE).[1-3] Systemic thrombolysis (ST) remains the current standard of care for high-risk PE and has been advocated[4] as the treatment of choice for select intermediate-risk patients.

Catheter-directed interventions (CDIs) have recently become popular for the treatment of acute high- and intermediate-risk PE because of the potential for

decreased bleeding complications compared with ST while providing similar efficacy in mortality and improvement in imaging parameters of heart strain. However, there is a paucity of direct comparative studies of CDI and ST. The expectation of lower rates of complications and similar effectiveness is based primarily on mechanistic similarities between CDI and ST but with less thrombolytic exposure with CDI, with supporting data from single-arm studies or comparisons with anticoagulation. Therefore, the objective of our study was to compare outcomes of CDI and ST in patients with massive or submassive PE using a large national database.

## METHODS

This study of deidentified national database data was approved and exempted from informed consent by the university Institutional Review Board (PRO15060452) before data acquisition and analysis.

Data for the study were acquired from the National Inpatient Sample (NIS) from 2009 to 2012. The NIS is a data set containing a 20% sample of nationwide inpatient discharges from U.S. hospitals collected and curated by the Agency for Healthcare Research Quality's Healthcare Cost and Utilization Project.[5] Before 2011, this was a collection of all discharges from a 20% sample of hospitals, but it transitioned to a 20% sample of all discharges with the 2012 data set, precluding further analysis of center volume data. Diagnoses and procedures were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding. Admission and discharge information including in-hospital mortality, length of stay, and hospital characteristics are hard-coded in the data. Nationwide population estimates were calculated using sampling weights provided by the Agency for Healthcare Research Quality to approximate nationwide hospital prevalence and incidence of these interventions.

Patients with acute PE were identified by ICD-9-CM coding (ICD-9 codes 415.11/13/19); both primary and secondary codes were used, increasing sensitivity of identification to include patients who may have developed acute PE after admission for another primary diagnosis. Clinical characteristics such as respiratory failure and hemodynamic shock were also identified using ICD-9 diagnosis codes.

Procedures were also identified using ICD-9-CM volume 3 coding. CDI does not have a unique ICD-9 code; the coding for endoluminal intervention (39.79) in the presence of a diagnosis of PE has been previously used,[6] and so it was incorporated in this study to identify CDI. In addition, procedure codes for invasive pulmonary angiography (88.43) in conjunction with a same-day administration of thrombolytic (99.10), in the absence of coronary or electrophysiology procedures, were used to identify catheter-directed thrombolysis.

**Comparative analysis.** The primary outcomes were in-hospital mortality, overall hemorrhagic complications, and hemorrhagic stroke. Secondary outcomes included additional hemorrhagic events, such as gastrointestinal bleed and clinically significant hematoma, as well as hospital length of stay and total charges.

Propensity matching was used to balance clinical and comorbid conditions.[7,8] A propensity model was specified using logistic regression on the odds of receiving CDI compared with ST (Supplementary Table, online only). The predicted probability was used as a propensity score to match CDI patients to ST patients with the same clinical and comorbid characteristics using 1:1 greedy matching. Validity of the model to create covariate balance between the matched groups was analyzed using significance testing and standardized differences, demonstrating adequate balancing across propensity-matched treatment groups (Supplementary Fig, online only). Sensitivity of the propensity model to an unmeasured confounder was assessed using the bounding method described by Rosenbaum.[9,10]

Exploratory subgroup analyses of high- and intermediate-risk patients were performed. High-risk PE patients were identified using ICD-9 coding of hemodynamic shock. Intermediate-risk patients, however, are more difficult to identify as classification is based on disease- and imaging-specific information not present in the NIS. By assuming that those receiving ST or CDI were either at high or intermediate risk (ie, no or very few low-risk patients would receive thrombolysis), removing the high-risk patients, and then matching ST patients to those remaining in the lysis cohort, matched subgroups were created approximating those at intermediate risk.

**Statistical methods.** Statistical analyses were performed using Stata SE 13.1 (StataCorp, College Station, Tex). Normality was assessed qualitatively. Unadjusted demographic and outcome comparisons were performed using $\chi^2$, Student $t$-test, Fisher exact, Wilcoxon rank sum, and Kruskal-Wallis testing where appropriate. Paired $t$-testing, McNemar test, standardized differences, and binomial-family generalized estimating equation regression with logit link and robust standard errors were used for analysis of matched outcomes.

## RESULTS

Using NIS data sets from 2009 to 2012, we identified 263,955 patient admissions with a diagnosis of acute PE. A minority (n = 5727) underwent treatment with ST or CDI; 4272 (75%) received ST and 1455 (25%) received CDI. The average age was 57.1 ± 16.7 years, and 50% were male. A quarter of patients had respiratory failure (n = 1500 [26%]), and 953 (17%) carried an ICD-9 diagnosis of hemodynamic shock. Compared with patients receiving ST, patients receiving CDI were significantly