Comparative Outcomes of Catheter-Directed Thrombolysis Plus Anticoagulation vs Anticoagulation Alone to Treat Lower-Extremity Proximal Deep Vein Thrombosis

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**Importance** The role of catheter-directed thrombolysis (CDT) in the treatment of acute proximal deep vein thrombosis (DVT) is controversial, and the nationwide safety outcomes are unknown.

**Objectives** The primary objective was to compare in-hospital outcomes of CDT plus anticoagulation with those of anticoagulation alone. The secondary objective was to evaluate the temporal trends in the utilization and outcomes of CDT in the treatment of proximal DVT.

**Design, Setting, and Participants** Observational study of patients with a principal discharge diagnosis of proximal or caval DVT from 2005 to 2010 in the Nationwide Inpatient Sample (NIS) database. We compared patients treated with CDT plus anticoagulation with the patients treated with anticoagulation alone. We used propensity scores to construct 2 matched groups of 3594 patients in each group for comparative outcomes analysis.

**Main Outcomes and Measures** The primary study outcome was in-hospital mortality. The secondary outcomes included bleeding complications, length of stay, and hospital charges.

**Results** Among a total of 90,618 patients hospitalized for DVT (national estimate of 449,200 hospitalizations), 3649 (4.1%) underwent CDT. The CDT utilization rates increased from 2.3% in 2005 to 5.9% in 2010. Based on the propensity-matched comparison, the in-hospital mortality was not significantly different between the CDT and the anticoagulation groups (1.2% vs 0.9%) (OR, 1.40 [95% CI, 0.88-2.25]) (P = .15). The rates of blood transfusion (11.1% vs 6.5%) (OR, 1.85 [95% CI, 1.57-2.20]) (P < .001), pulmonary embolism (17.9% vs 11.4%) (OR, 1.69 [95% CI, 1.49-1.94]) (P < .001), intracranial hemorrhage (0.9% vs 0.3%) (OR, 2.72 [95% CI, 1.40-5.30]) (P = .03), and vena cava filter placement (34.8% vs 15.6%) (OR, 2.89 [95% CI, 2.58-3.23]) (P < .001) were significantly higher in the CDT group. The CDT group had longer mean (SD) length of stay (7.2 [5.8] vs 5.0 [4.7] days) (OR, 2.27 [95% CI, 1.49-1.94]) (P < .001) and higher hospital charges ($85,094 [$69,121] vs $28,164 [$42,067]) (P < .001) compared with the anticoagulation group.

**Conclusions and Relevance** In this study, we did not find any difference in the mortality between the CDT and the anticoagulation groups, but evidence of higher adverse events was noted in the CDT group. In the context of this observational data and continued improvements in technology, a randomized trial with outcomes such as mortality and postthrombotic syndrome is needed to definitively address this comparative effectiveness.

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Deep vein thrombosis (DVT) is the third most common cause of cardiovascular morbidity and mortality after coronary artery disease and stroke, and it occurs in about 1 person per 1000 population per year. Proximal DVT is defined as a DVT involving the popliteal vein or above and accounts for approximately 80% of all DVT cases. Deep vein thrombosis has been associated with significant early mortality with death rates of approximately 6% within 1 month of the diagnosis.

Approximately 20% to 50% of patients with proximal DVT will go on to develop postthrombotic syndrome (PTS) in spite of current therapies with anticoagulation and compression stockings. Pain, swelling, heaviness, edema, skin pigmentation, and in severe cases, ulcerations characterize this syndrome. Postthrombotic syndrome markedly impairs the quality of life of these patients and is a significant economic burden on society. In fact, the quality-of-life impairment of patients with PTS parallels that of those with severe chronic obstructive pulmonary disease, congestive heart failure, or angina pectoris.

Several studies have shown that early thrombus removal by catheter-directed thrombolysis (CDT) leads to a significant reduction in the incidence of PTS along with improvements in quality-of-life parameters in a cost-effective fashion. Unfortunately, owing to the small number of patients in these studies, the comparative safety outcomes were inconclusive. This controversy is reflected in conflicting societal guideline recommendations, with the American College of Chest Physicians recommending against the use of CDT, mostly because of concern for its safety and complexity, while the American Heart Association recommends CDT as first-line therapy for low bleeding risk patients with iliofemoral DVT. In light of these conflicting directives, we sought to assess real-world comparative safety outcomes in patients with proximal and caval DVT who underwent CDT plus anticoagulation with a group treated with anticoagulation alone using risk-adjusted propensity score matching. We also evaluated the temporal trends in CDT utilization and outcomes in the United States from 2005 to 2010.

Methods
The Temple University School of Medicine institutional review board approved the study, waiving participant informed consent for this retrospective database review.

Study Data
The study data were obtained from the Nationwide Inpatient Sample (NIS) files of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project for treatment rendered and outcomes recorded between January 2005 and December 2010. The authors designed the study and are responsible for analyzing the data and for the accuracy of the analysis presented.

The NIS is an all-payer, administrative claims-based database, which contains information about patient discharges from about 1000 nonfederal acute-care hospitals in 45 states across the United States. The NIS contains clinical and resource utilization information on approximately 5 to 8 million hospital discharges each year, which represent 20% of US inpatient hospitalizations. Using an AHRQ sampling and weighting method, we used the data to calculate national estimates of the entire US population of hospitalized patients.

Study Population
Patients with a principal discharge diagnosis of proximal lower-extremity DVT (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 453.41) or inferior vena cava DVT (ICD-9-CM code 453.2) were identified in the NIS database. These patients were stratified according to use of thrombolytic therapy (ICD-9-CM procedure code 99.10). Since systemic thrombolysis is rarely used in the treatment of acute DVT, and we did not include patients with a principal discharge diagnosis of pulmonary embolism (ICD-9-CM code 415.1), we hypothesized that these patients were treated with CDT plus anticoagulation with or without mechanical thrombectomy. We compared baseline characteristics of this group with those of patients who did not receive any thrombolytic agents, and we assumed that all patients in this group were treated with anticoagulation alone. We also evaluated temporal trends in the utilization rates of CDT from January 2005 to December 2010. All data used for trend analysis were derived from national weighted estimates. We used multivariate analysis to identify predictors of adverse outcomes in patients undergoing CDT.

We excluded patients who were younger than 18 years and those for whom the age information was missing. We did not include patients diagnosed as having 1 or more of the following conditions: isolated distal lower-extremity DVT (ICD-9-CM code 453.42), pregnancy-related DVT (ICD-9-CM codes 671.3, 671.4, and 671.9), or unspecified lower-extremity DVT (ICD-9-CM code 453.40).

Comparative Outcomes Analysis
We anticipated that the CDT group would be different from the anticoagulation group with respect to comorbid and demographic characteristics. To adjust for these confounding variables and to reduce the effect of selection and indication bias, we used propensity matching to derive the 2 matched groups for comparative outcomes analysis. A nearest neighbor 1:1 variable ratio, parallel, balanced propensity-matching method was used after generating the propensity scores from 44 clinical, hospital, and demographic covariates including the Elixhauser comorbidity index (eTable 7 in the Supplement). The primary end point was in-hospital mortality, and the secondary end points included pulmonary embolism, blood transfusion, gastrointestinal bleeding, intracranial bleeding, procedure-related hematomas, inferior vena cava filter placement, length of stay, and hospital charges.

Statistical Analysis
Descriptive summary statistics are presented as means (SDs) for continuous variables and as frequencies with percentages for categorical variables. Baseline characteristics were compared between the 2 groups using an independent sample t test.
Comparison of Treatments for Deep Vein Thrombosis

Results

Characteristics of the Study Population

Between January 2005 and December 2010, a total of 90 618 patients with a principal discharge diagnosis of lower-extremity proximal or caval DVT were identified in the NIS database, representing a national estimate of 449 200 cases. There was a cohort of 3649 patients (4.1%), representing a national estimate of 17 975 patients who underwent CDT (eFigure 1 in the Supplement). The baseline characteristics of the study patients are listed in Table 1.

Trends in the Utilization and Outcomes of Catheter-Directed Thrombolysis

During the 6-year study period, there was a low rate (4.1%) of CDT utilization with a steady increase noted from 2.3% in 2005 to 5.9% in 2010 (Figure 1). Most CDT procedures (94.8%) were performed within the first 6 days of hospitalization (median procedure day, 1.0; mean procedure day, 2.0). The groups less likely to be treated with CDT included women (3.8% vs 4.6% for men) (P < .001), patients older than 65 years (2.0% vs 6.4% for younger patients) (P < .001), and African American and Hispanic minorities (3.1% vs 4.2% for whites) (P < .001). The patients with private third-party insurance had higher CDT rates than self-pay patients or those with Medicare or Medicaid (7.3% vs 2.8%) (P < .001). Catheter-directed thrombolysis was more likely to be performed in urban centers (4.4% vs 1.4% for nonurban centers) (P < .001) and academic centers (5.2% vs 3.2% for nonacademic centers) (P < .001).

The in-hospital mortality rate decreased from 1.3% in 2005 to 1.0% in 2010 (P < .005; Figure 2A). The in-hospital mortality was significantly lower in centers with institutional volume of more than 5 CDT cases per year than in those centers with institutional volume of 5 or fewer CDT cases a year (0.6% vs 1.6%) (P = .01). In patients undergoing CDT, the venous angioplasty rate was 57.7%, and 26.3% had stents implanted. The temporal trends in blood transfusion, inferior vena cava filter placement, length of hospital stay, and hospital charges are shown in Figure 2. In the CDT group, the following characteristics were noted to be significant predictors of death or intracranial hemorrhage: (1) shock, (2) cancer, (3) paralysis, (4) age greater than 75 years, (5) Hispanic ethnicity, (6) CDT performed at a center with low institutional volume, (7) renal failure, and (8) congestive heart failure (eFigure 2 in the supplement).

Characteristics and Outcomes of Propensity-Matched Groups

The propensity score matching algorithm yielded 3594 well-matched patients in each group, with a C statistic of 0.828 (eFigure 3 in the Supplement). The key baseline characteristics are listed in Table 1, and the in-hospital clinical outcomes including mortality differences between the 2 groups are listed in Table 2. The adjusted in-hospital mortality rates were not significantly different between the CDT group and the anticoagulation group (1.2% vs 0.9%) (OR, 1.4 [95% CI, 0.88-2.25]) (P = .15). The rates of blood transfusion (11.1% vs 6.5%) (P < .001), pulmonary embolism (17.9% vs 11.4%) (P < .001), intracranial hemorrhage (0.9% vs 0.3%) (P = .03), and vena cava filter placement (34.8% vs 15.6%) (P < .001) were significantly higher in the CDT group. The CDT group had longer mean (SD) hospital stay (7.2 [5.8] days vs 5.0 [4.7] days) (P < .001) and higher hospital charges ($85 094 [69 121] vs $82 164 [42 067]) (P < .001) than the anticoagulation group. (The outcomes with the Cox model with IPTW using the procedure day of CDT as a time-dependent covariate and unmatched outcomes are reported in the Supplement.)

Sensitivity Analysis

Using the rule-out approach, we estimated that for an unmeasured confounder to fully explain our outcome differences in pulmonary embolism, this confounder would have to be 3 times more likely to be associated with CDT use than with anticoagulation and would itself have to increase the risk of the outcome by 8.5 times (eFigure 4 in the Supplement). For all significant results between other outcomes (eg, blood transfusion) and CDT use detailed in Table 2, only under even more extreme conditions could the results be fully explained by an unmeasured confounder. Our results were similar in all the other comparative analytic methods used (Cox regression for continuous variables and using the Pearson χ² test for categorical variables. We evaluated trends in the utilization rates and outcomes using the Cochran-Armitage trend test. We performed multivariate logistic regression analysis to determine predictors of a composite end point of death or intracranial hemorrhage in patients undergoing CDT after adjusting for the calendar year.

Most categorical variables, including patient sex, hospital location, and hospital teaching status, had less than 1% missing data and were imputed to the most common category. Race had 19.6% missing data, and since we did not consider race to be a major factor affecting the outcomes, and to preserve the full sample size, we used a dummy variable adjustment method and then adjusted the propensity-matched outcomes for race.

To control for potential differences between CDT and anticoagulation groups, we conducted propensity score 1:1 matched analysis and incorporated the matching into statistical analyses. We used multivariate logistic regression to estimate race-adjusted odds ratios (ORs) and 95% CIs for the association between CDT use and each end point compared with the propensity-matched anticoagulation group. To account for the immortal time bias, we used propensity score–based inverse probability of treatment weighting (IPTW) in a Cox model with the outcome of death using the procedure day of CDT as a time-dependent covariate. We also performed our comparative safety analysis using 1:5 greedy matching and propensity score–adjusted logistic regression analysis. Finally, we used a rule-out approach to sensitivity analysis to illustrate how strongly a single unmeasured binary confounder would have to be associated with both CDT use and the end point to fully explain our significant findings. All statistical analysis was performed using SPSS software, version 20 (IBM Corporation) and SAS software, version 9.3 (SAS Institute Inc).
model with IPTW and a time-dependent covariate, 1:5 greedy matching, and propensity score-adjusted logistic regression analysis).

### Discussion

To our knowledge, this is the first large nationwide observational study that addresses safety outcomes of CDT in patients with acute proximal lower extremity and caval DVT. This propensity-matched comparative effectiveness analysis shows that in-hospital mortality was not significantly different between the CDT group and the anticoagulation group. The in-hospital mortality in the CDT group significantly declined during the 6 study years, while the in-hospital morbidity in the CDT group continues to be higher.

Several small studies, including 2 randomized trials, have suggested that CDT leads to significant reduction in PTS as well as improvement in venous function.\(^1^9^{–26}\) but the widespread adoption of this form of therapy has been limited by its safety
Data from a US registry of 473 patients treated with CDT showed a mortality rate of 0.4%, major bleeding rate of 11%, and an intracranial bleeding rate of 0.4%. Recently, a randomized trial of 209 patients reported a clinically significant bleeding rate of 9%, mostly related to the access site, without any deaths, pulmonary emboli, or intracranial hemorrhages. Most of these studies have shown low mortality (<1%) following CDT. However, owing to small sample sizes, clinicians are often not comfortable relying on these data to recommend treatment that might reduce the incidence of PTS, a disabling but nonfatal condition, at the cost of a potentially life-threatening bleeding complication. Unfortunately, this safety concern has been difficult to address because of a low incidence of adverse events and a need for a large sample size to evaluate differences between the 2 treatment groups. In fact, the ongoing ATTRACT trial may not have enough acute adverse events to detect this difference.

The decreasing in-hospital mortality in the CDT group over the study period may reflect a learning curve, and use of newer pharmacomechanical therapies may result in lower doses and shorter durations of use of thrombolytic agents. In fact, during the last 2 years of our study period, the in-hospital mortality was similar between the 2 treatment groups. This is corroborated by the significantly greater decrease in hospital length of stay in the CDT group vs the anticoagulation group ($P < .001$) over the 6-year study period. However, the bleeding complications including intracranial hemorrhage and blood transfusion rates continued to be higher in the CDT group.
The utilization rates for CDT in the United States increased during the 6-year study period, but the absolute rate was still low (4.1%). A duplex ultrasonography study36 showed that approximately 26% of these patients should be eligible for CDT. Even in patients with caval DVT, fewer than 1 in 5 patients received CDT. Our study showed that angioplasty and stenting rates in the United States are higher in these patients than in those reported from Europe.37

High rates of inferior vena cava filter placement in the CDT group is concerning because there is no clear benefit of these devices documented in these patients.38–40 Several studies indicate that symptomatic pulmonary embolism is uncommon (incidence, about 1%) and rarely fatal (<0.2%) in patients undergoing CDT.41–43 Since our study also showed that there is significantly higher initial resource utilization associated with CDT (increased length of stay and hospital charges), it is crucial that rigorous economic analyses from ongoing and completed randomized trials be incorporated into future guideline recommendations.

Our study had several limitations. First, the potential for unmeasured confounding may bias the result in either direction: perhaps patients with larger, more dangerous clots were selected for CDT, or alternatively, more stable patients were selected to undergo CDT. However, we believe that this selection bias was addressed by rigorous propensity score matching, which was further validated by our sensitivity analysis. Second, accurate quantification of adverse events other than in-hospital mortality and blood transfusion rates may be lacking owing to coding inaccuracies. However, we believe that comparative analysis is fairly reasonable after propensity matching between the 2 treatment groups, with the potential caveat of overestimating the adverse events such as pulmonary embolism in both groups. Third, the comparative outcomes of CDT in patients with iliofemoral DVT vs femoropopliteal DVT could not be assessed in our study because these conditions are not coded separately in the ICD-9-CM. However, we had similar results in both caval and noncaval DVT.

In addition, this analysis is based on hospital claims and not medical record review, hence is potentially subject to the shortcomings of an administrative data set.44 We addressed this limitation by including only those patients who had a principal discharge diagnosis of proximal or caval DVT, which has a high positive predictive value (>95%) compared with medical record reviews.43 Furthermore, our analysis was limited to hospitalized patients and we cannot be sure that these results will hold true for patients who are treated as outpatients. It is also possible that some hospitalized patients with DVT were not anticoagulated at all, but we believe that is a very small minority of patients. In fact 1 study showed that more than 99% of symptomatic patients with proximal DVT are anticoagulated.44 Finally, the NIS does not provide information about survival beyond the inpatient period; hence, longer-term outcomes are unknown.

Table 2. Outcomes of Patients Undergoing CDT Plus Anticoagulation or Anticoagulation Alone in Propensity-Matched Groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CDT* (n = 3594)</th>
<th>Anticoagulation* (n = 3594)</th>
<th>OR (95% CI)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>42 (1.2)</td>
<td>31 (0.9)</td>
<td>1.41 (0.88-2.25)</td>
<td>.15</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>642 (17.9)</td>
<td>408 (11.4)</td>
<td>1.69 (1.49-1.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>397 (11.1)</td>
<td>234 (6.5)</td>
<td>1.85 (1.57-2.20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>GI bleed</td>
<td>59 (1.6)</td>
<td>56 (1.6)</td>
<td>1.08 (0.75-1.57)</td>
<td>.67</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>32 (0.9)</td>
<td>12 (0.3)</td>
<td>2.72 (1.40-5.30)</td>
<td>.03</td>
</tr>
<tr>
<td>Hematoma</td>
<td>86 (2.4)</td>
<td>20 (0.6)</td>
<td>4.54 (2.78-7.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IVC filters</td>
<td>1250 (34.8)</td>
<td>561 (15.6)</td>
<td>2.89 (2.58-3.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of stay, mean (SD), d</td>
<td>7.23 (5.80)</td>
<td>5.02 (4.67)</td>
<td>2.27 (1.49-1.94)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Charges, mean (SD), $</td>
<td>85,094 (69,121)</td>
<td>28,164 (42,067)</td>
<td>57,417 (54,796-60,037)c</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CDT, catheter-directed thrombolysis; GI, gastrointestinal; IVC, inferior vena cava; OR, odds ratio.

a Unless otherwise indicated, data are reported as number (percentage) of patients.
b Odds ratio adjusted for race.
c Estimated difference between the 2 groups.

Conclusions

The results of this study suggest that rates of bleeding complications are higher with CDT, despite technological and pharmacological advances, and so this therapy should be offered only to patients with a low bleeding risk.27 At present, there is lack of sufficient evidence to suggest that similar outcomes would have been noted if our study were restricted to patients with iliofemoral DVT. In light of the findings of this study, it is imperative that the magnitude of benefit from CDT be substantial to justify the increased initial resource utilization and bleeding risks of this therapy. However, our study is reassuring in that the acute mortality rate was not higher with CDT than with anticoagulation, particularly in centers that perform more than 5 procedures a year.

In summary this nationwide observational study shows that in-hospital mortality associated with CDT has been improving during recent years, and in fact the mortality in the last 2 years of the study period was similar to that in the anticoagulation group. Despite a lack of clear benefit of inferior vena cava filter placement, a substantial percentage of US patients are still having these devices placed. In addition, CDT continues to be associated with greater in-hospital morbidity and bleeding rates than anticoagulation alone. Since our results are based on observational data, our findings could be subject to residual confounding, which further highlights the need for randomized trial evidence to evaluate the magnitude of the effect of CDT on outcomes such as mortality, PTS, and recurrence of DVT. In the absence of such data, it may be reasonable to restrict this form of therapy to those patients who have a low bleeding risk and a high risk for PTS, such as patients with iliofemoral DVT.
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Study concept and design: Bashir, Zack, Bove.
Acquisition, analysis, or interpretation of data: Bashir, Zack, Zhao, Comerota, Bove.
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REFERENCES


