

From the Midwestern Vascular Surgical Society

## Evaluation of thrombolysis using tissue plasminogen activator in lower extremity deep venous thrombosis with concomitant femoral-popliteal venous segment involvement

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### ABSTRACT

**Objective:** Current guidelines recommend thrombolytic therapy for iliofemoral deep venous thrombosis (DVT). Anticoagulation is the standard treatment for femoral-popliteal and tibial-level DVT. The objective of this study was to evaluate the efficacy of catheter-directed thrombolysis (CDT) using tissue plasminogen activator vs standard anticoagulation alone in patients with lower extremity DVT involving the femoral-popliteal segment.

**Methods:** A retrospective review was performed of patients referred to the vascular surgery service with lower extremity DVT from 2006 to 2015. Patients who had DVT involving the femoral-popliteal segment were identified, including some patients who had concomitant involvement of iliofemoral and tibial veins. Patients with pure iliofemoral and tibial vein DVT were excluded from this analysis. Review of medical records, follow-up ultrasound studies, hypercoagulable panel, and venography were performed. Comparison of outcomes between patients who received thrombolytic therapy using tissue plasminogen activator and patients who received standard anticoagulation alone was performed. The primary outcomes measured were restoration of patency of the femoral-popliteal segment at 3 months, incidence of post-thrombotic syndrome (PTS), and valvular dysfunction. Secondary outcomes were incidence of bleeding, in-hospital mortality, and pulmonary embolism.

**Results:** The study cohort was composed of 191 patients (CDT,  $n = 89$ ; anticoagulation alone,  $n = 102$ ) who met inclusion criteria. Most patients with thrombus involving the femoral-popliteal segment also had proximal venous segment involvement, with 93% of the patient cohort having proximal iliofemoral DVT. Patients who did not receive CDT were older (mean age of 64 years vs 51 years;  $P < .001$ ) and had more associated comorbidities, such as diabetes, immobility, and cancer. A significant number of patients who received CDT had a positive family history for DVT (21.3% vs 8.8%;  $P = .023$ ), and it was more likely to be their first episode of DVT (73.0% vs 55.9%;  $P = .016$ ). Patients who received CDT were more likely to have restoration of patency (74.7% vs 11.1%;  $P < .001$ ) and lower incidence of PTS (21.3% vs 73.4%;  $P < .001$ ) and valvular dysfunction (23.0% vs 66.7%;  $P < .001$ ) compared with patients who were treated with anticoagulation alone. Incidence of bleeding was significantly more for patients treated with anticoagulation alone (14.7% vs 5.6%;  $P = .018$ ) compared with patients who received CDT. On multivariate analysis, age was the predominant risk factor for bleeding. There was no significant difference in mortality and pulmonary embolism.

**Conclusions:** In patients with acute proximal DVT and concomitant femoral-popliteal venous segment involvement, CDT resulted in superior patency at 3 months and less PTS and valvular reflux. This was achieved without increase in bleeding complications compared with anticoagulation alone. Age was the major factor predictive of bleeding in either group. The results of this study may not be applicable to patients with pure femoral-popliteal venous segment DVT because only 3% of patients had this finding. (*J Vasc Surg: Venous and Lym Dis* 2017;■:1-8.)

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Deep venous thrombosis (DVT) is a major health problem that occurs in about 1 person per 1000 population per year, making it the third most common cause of cardiovascular morbidity and mortality after coronary artery disease and stroke.<sup>1-3</sup> Venous thromboembolic disease is an underdiagnosed disease associated with high mortality and morbidity from pulmonary embolism (PE) and post-thrombotic syndrome (PTS), leading to chronic limb ailments.

Up to 50% of patients diagnosed with DVT eventually develop PTS, despite receiving treatment with anticoagulation and compression therapy.<sup>4,5</sup> PTS is manifested by some degree of pain, calf swelling, heaviness, edema,

skin pigmentation, or venous ulceration of the affected leg, with symptoms becoming apparent usually within the first 2 years after the thrombotic event.<sup>6</sup> Multiple studies have shown that PTS is a progressive disease that can lead to venous ulceration despite optimal treatment with compression stockings.<sup>7-10</sup> Venous ulceration results in significant disability and decreased quality of life for those patients afflicted.<sup>11,12</sup>

The American College of Chest Physicians (CHEST) societal guidelines outline the current standard of care for treatment of DVT, placing emphasis on the traditional approach with parenteral and oral anticoagulation.<sup>13</sup> However, these recommendations were made primarily because of the lack of good-quality evidence to suggest otherwise. Several small studies have shown that early thrombus removal by catheter-directed thrombolysis (CDT) leads to a significant reduction in the incidence of PTS and an overall improvement in quality of life.<sup>14-17</sup> Unfortunately, because of small sample sizes in these studies, the comparative safety outcomes between standard anticoagulation and CDT remained inconclusive.<sup>18</sup> The most recent CHEST guidelines state that "anticoagulation therapy alone is an acceptable alternative to CDT in all patients with acute lower extremity DVT," citing unacceptable risk of bleeding.<sup>13,18-20</sup> In contrast to the CHEST guidelines, the American Heart Association does recommend CDT as first-line therapy for patients at low bleeding risk with lower extremity DVT. However, this recommendation was only for DVT occurring within the iliofemoral segment.<sup>21</sup>

In light of the conflicting directives, the current role of CDT for lower extremity DVT remains unclear. Whereas CDT has been used for DVT involving the iliofemoral segment, the results are as yet unknown when the DVT involves the femoral-popliteal segment. The objective of this study was to evaluate the efficacy of CDT using tissue plasminogen activator (tPA) vs standard anticoagulation alone in the treatment of patients with lower extremity DVT in which the femoral-popliteal venous segment was involved. The hypothesis was that patients who received CDT would have superior patency, less valve dysfunction, and less PTS. Secondary outcomes evaluated were PE, risk of bleeding, and mortality in the two groups.

## METHODS

**Study design.** The Mercy Medical Center Institutional Review Board approved this study, waiving participant informed consent. A retrospective evaluation was performed of all patients referred to the vascular surgery service of Mercy Medical Center (Des Moines, Iowa) who were diagnosed with lower extremity DVT (*International Classification of Diseases, Ninth Revision* code 453.40) from January 1, 2006, to June 30, 2015. Review of inpatient and outpatient medical records and ultrasound and venography reports was performed. The protocol

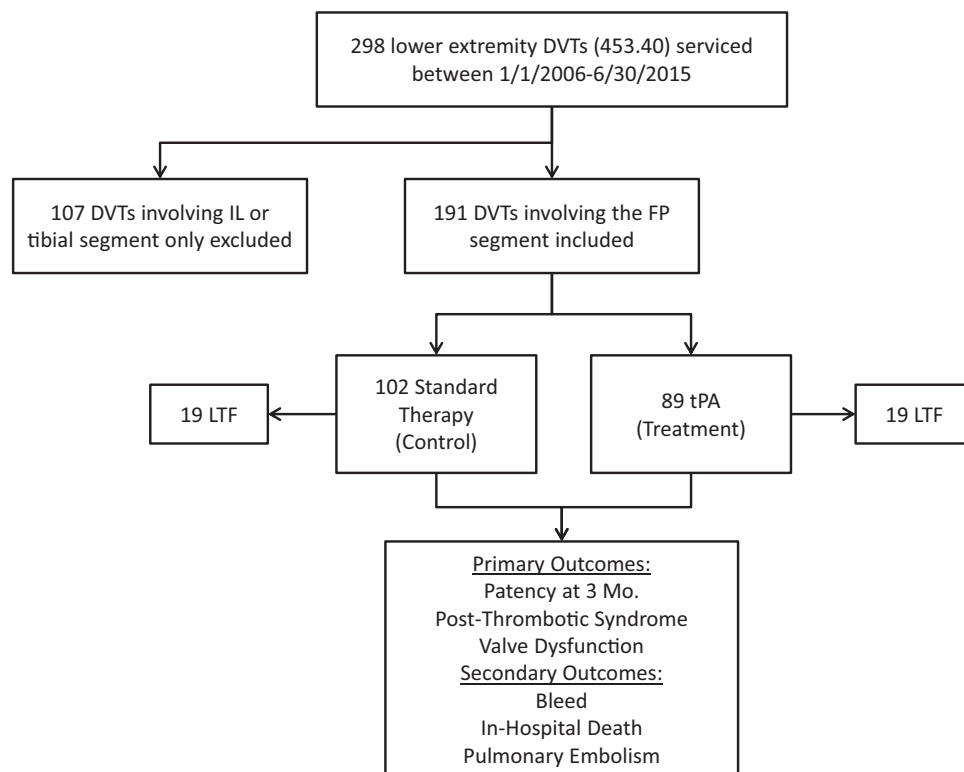
## ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective single-center case-control study
- **Take Home Message:** In this study, 89 patients with deep venous thrombosis (DVT) involving the femoral-popliteal venous segment who underwent catheter-directed thrombolysis had superior outcomes at 3 months compared with 102 patients who were treated with standard anticoagulation alone; 93% of the patients also had iliofemoral DVT. This was achieved without increase in bleeding complications.
- **Recommendation:** The authors suggest using catheter-directed thrombolysis for treatment of femoral-popliteal acute DVT if there is no contraindication and there is associated iliofemoral DVT.

for follow-up was 1 month, 3 months, and 6 months. The venous segments involved were classified as iliofemoral (at or above the inguinal ligament), femoral-popliteal (common femoral, femoral, and popliteal veins), and tibial veins (below popliteal veins). For this analysis, patients with DVT involving isolated iliofemoral or tibial veins were excluded (Fig 1).

Primary outcomes evaluated were venous patency at 3 months, incidence of PTS, and presence of valvular dysfunction on ultrasound. Three months of follow-up was the most accurate data point to report, given that >75% of patients in the standard anticoagulation group and >90% of patients in the CDT group had ultrasound follow-up at 3 months. Venous patency was evaluated by ultrasound, which looked at the lower extremity from the level of the groin downward to the ankle, and defined as either complete or partial restoration of the lumen of the femoral-popliteal venous segment. Patency of the iliofemoral segment was not routinely evaluated but was indirectly suggested by phasic flow at the common femoral vein level. However, data were inconsistent, and this result was thus not reported. The presence of PTS was guided by the Villalta scale, but the severity was not graded in this study.<sup>22,23</sup> For the purposes of this study, the diagnosis of PTS was determined by the presence of at least five symptoms or clinical signs as described by the Villalta score descriptors. The venous reflux examination protocol measures valve reflux at the common femoral, superficial femoral, and popliteal levels. Valvular reflux was defined by venous reflux ultrasound showing the presence of valve reflux >1 second.

Secondary outcomes evaluated were major and minor bleeding complications during the index hospitalization. Major bleeding complications included intracranial bleed, gastrointestinal bleed, and transfusion requirement of 2 units or more of packed red blood cells. Minor bleeding complications included sheath hematoma and



**Fig 1.** Overall study design. Patients (N = 298) were selected on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code 453.40 during January 1, 2006, to June 30, 2015. If lower extremity deep venous thromboses (DVTs) involved the iliofemoral (IL) or tibial segment only, patients (n = 107) were excluded from the study. There were 89 patients in the treatment group (those who received tissue plasminogen activator [tPA] treatment) and 102 patients in the control group (those who received standard anticoagulation treatment only). FP, Femoral-popliteal; LTF, loss to follow-up.

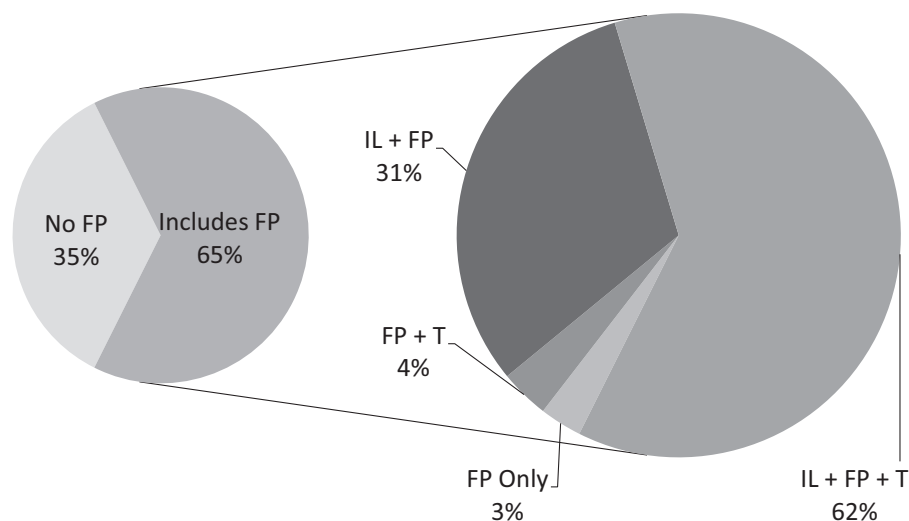
ecchymosis. Other secondary outcomes were in-hospital mortality and incidence of PE.

**Procedure for standard anticoagulation.** Patients in the anticoagulation group were treated with either initial parenteral unfractionated heparin at standard dosing to keep anti-factor Xa levels between 0.3 and 0.7 IU/mL or standard dose low-molecular-weight heparin (enoxaparin at 1 mg/kg twice daily), followed by initiation of oral anticoagulation therapy with either warfarin or rivaroxaban.

**Procedure for CDT.** With the patient prone, the popliteal vein of the index limb was accessed under ultrasound guidance using a micropuncture kit (Cook Medical, Bloomington, Ind), and a short 6F sheath was placed. Initial venography was performed through a 5F Berenstein catheter (AngioDynamics, Latham, NY) to demonstrate the extent and length of thrombus. If a patent segment of vein in the upper calf or lower popliteal region below the thrombosed segment was available, that was preferred for access, but otherwise direct access into clot was acceptable. Inferior vena cava filtration was not typically used unless mobile-appearing clot or other indications warranted. An infusion catheter with multiple

side holes was then placed across the thrombus with complete coverage of the occluded segment if possible. Typically, a 40-cm catheter was used (Uni\*Fuse Infusion Catheter; AngioDynamics), covering from the popliteal access site to near the common femoral-external iliac vein region. If additional thrombus extended into the iliac vein and the inferior vena cava, an ev3 ProStream infusion wire (Medtronic, Minneapolis, Minn) that provided infusion through side holes in the guidewire over an additional 12-cm length was used.

Alteplase (tPA) has been the standard thrombolytic agent used in our institution. In our early experience, we had used an 8-mg bolus of alteplase diluted in 20 mL of 0.9% NaCl given through the catheter into the clot during 20 minutes, followed by a continuous infusion at 0.5 mg/h. If an infusion wire was used, the alteplase was infused at a rate of 0.25 mg/h. Also, if the infusion catheter was placed with the infusion length beginning away from the tip of the sheath to obtain longer coverage, an additional infusion of alteplase through the sheath of 0.25 mg/h was added. In general, the total maximum dose was kept at or below 1 mg/h by adjusting the dosing in the other sites. More recently, the bolus dose had been reduced to 4 mg of alteplase, given



**Fig 2.** Lower extremity deep venous thrombosis (DVT) segmental breakdown. There were 35% of patients who did not have lower extremity DVT involving the femoral-popliteal (FP) segment. Of the 65% of patients who had lower extremity DVT that involved the FP segment, only 3% were FP only. *IL*, Iliofemoral; *T*, tibial.

our observation that an increasing incidence of dropping fibrinogen levels may have been related to the previously more aggressive bolus dose. If fibrinogen levels were  $<150$  mg/dL, the tPA infusion dose was halved; and if fibrinogen levels were  $<100$  mg/dL, the tPA infusion was discontinued altogether. If not already initiated, heparinization without bolus was instituted, although the majority of patients would have been started on heparin intravenous infusion before the initiation of CDT, as is standard practice at our institution. Standard heparin infusion was monitored with anti-factor Xa levels, titrated to a therapeutic range of 0.3 to 0.7 unit/mL.

After the initiation of lysis, clot burden at the start of CDT and during thrombolysis was assessed daily by venography until the completion of lysis or intervention was indicated. Adjunctive procedures, such as AngioJet thrombectomy (Boston Scientific, Marlborough, Mass), balloon angioplasty, and stenting, were performed as needed. Attempts to limit infusion to  $<3$  days were preferred, given increased risk of bleeding with longer time frames. After discharge from the hospital, patients were seen during clinic visits within 3 months and again at 6 months. Unless it was contraindicated, the majority of patients were maintained on anticoagulation for at least 6 months. Patients with thrombophilia or repeated episodes of DVT were maintained on lifelong anticoagulation.

**Postprocedure adjuncts.** All patients received postprocedure adjuncts of ambulation and venous knee- or thigh-high compression stockings, depending on the level of involvement, with a strength varying from 20 to 40 mm Hg, depending on severity of symptoms and the patient's tolerance.

**Statistical analysis.** Based on the data collected from the systematic review of patient records as outlined before, univariate analysis was performed on demographic and clinical characteristics, primary outcomes, and secondary outcomes. Discrete variables were tested with two-sided Fisher exact test, and the continuous variable was tested with two-sided Student *t*-test. Because the significant demographics and clinical characteristics associated with each of the outcomes examined with multivariate analysis were unknown, logistic regression was performed with an automated model selection with stepwise backward selection starting with all significant characteristics as identified by the univariate analysis, which included age, diabetes, cancer, immobility, family history, and first episode. With each iteration of the model selection process, factors with the highest *P* value above .05 were removed from the final logistic regression model. Survival analyses were based on Kaplan-Meier estimation from the date of the last known status for each of the primary outcomes for 48 months. Patients were considered to be lost to follow-up if they never returned after the initial diagnosis visit. Stata software (version 12; StataCorp LP, College Station, Tex) was used for all analyses. Findings with *P* values  $< .05$  were considered to be statistically significant.

## RESULTS

During January 1, 2006, to June 30, 2015, 298 patients diagnosed with lower extremity DVTs were identified (Fig 1). For this study, 35% of the patients were excluded because of pure iliofemoral or tibial segment involvement. This left 65% of patients ( $n = 191$ ), who formed the study cohort (Fig 2). Most patients with thrombus involving the femoral-popliteal segment also had

**Table I.** Demographic and clinical characteristics

	tPA (n = 89)	Standard anticoagulation alone (n = 102)	P value
Age, years, mean (SD)	51.6 (16.5)	64.2 (16.8)	<.001
Female gender	44 (49)	47 (46)	.665
Obese (BMI >30)	50 (56)	47 (46)	.192
Diabetes mellitus	14 (16)	34 (33)	.007
Cancer	9 (10)	33 (32)	<.001
Immobility	23 (26)	47 (46)	.004
Family history	19 (21)	9 (9)	.023
First episode	65 (73)	57 (56)	.016
Thrombophilia	44 (49)	25 (25)	<.001

BMI, Body mass index; SD, standard deviation; tPA, tissue plasminogen activator.  
Values are reported as number (%) unless otherwise indicated.

concomitant involvement of the iliofemoral and tibial segments. Only 3% of the patients had isolated femoral-popliteal DVT (Fig 2). The study group was then separated into treatment (CDT, n = 89) and control (standard anticoagulation alone, n = 102) groups. The median follow-up for evaluation of primary outcomes was 17 months for the group receiving CDT and 8 months for the group receiving anticoagulation alone. There was an equal number of patients who were lost to follow-up in each group (n = 19).

Table I shows the demographic and clinical characteristics of the 191 patients. Patients in the CDT group were significantly younger (51 vs 64 years;  $P < .001$ ), more likely to have a positive family history for DVT (21.3% vs 8.8%;  $P = .023$ ), more likely to have a first episode of DVT (73.0% vs 55.9%;  $P = .016$ ), and more likely to have an inherited or acquired thrombophilia as proven by a positive hypercoagulability workup (49.4% vs 24.5%;  $P < .001$ ). In contrast, patients in the control group were more likely to be diabetic (33.3% vs 15.7%;  $P = .007$ ), to have cancer (32.3% vs 10.1%;  $P < .001$ ), and to be immobile (46.1% vs 25.8%;  $P = .004$ ). Patients were classified as immobile if they had any history of inactivity in the preceding month from the date of diagnosis of DVT. There was no significant difference in gender or body mass index between the two groups.

Patients in the treatment group were more likely to have restoration of patency of the femoral-popliteal venous segment at 3 months (74.7% vs 11.1%;  $P < .001$ ) and to have lower incidence of PTS (21.3% vs 73.4%;  $P < .001$ ) as well as of valvular dysfunction (23.0% vs 66.7%;  $P < .001$ ) compared with the control group (Table II). The model selection has chosen first episode of DVT and tPA use as the predictors of patency at 3 months, and the treatment group had a >21 times (95% confidence interval [CI], 8.8-51.3;  $P < .001$ ) increase of odds to remain patent at 3 months. CDT with tPA

**Table II.** Primary outcomes

	tPA, No. (%)	Standard anticoagulation alone, No. (%)	P value
Patency at 3 months	56 of 75 (75)	9 of 81 (11)	<.001
PTS	16 of 75 (21)	47 of 64 (73)	<.001
Valve dysfunction	14 of 61 (23)	14 of 21 (67)	<.001

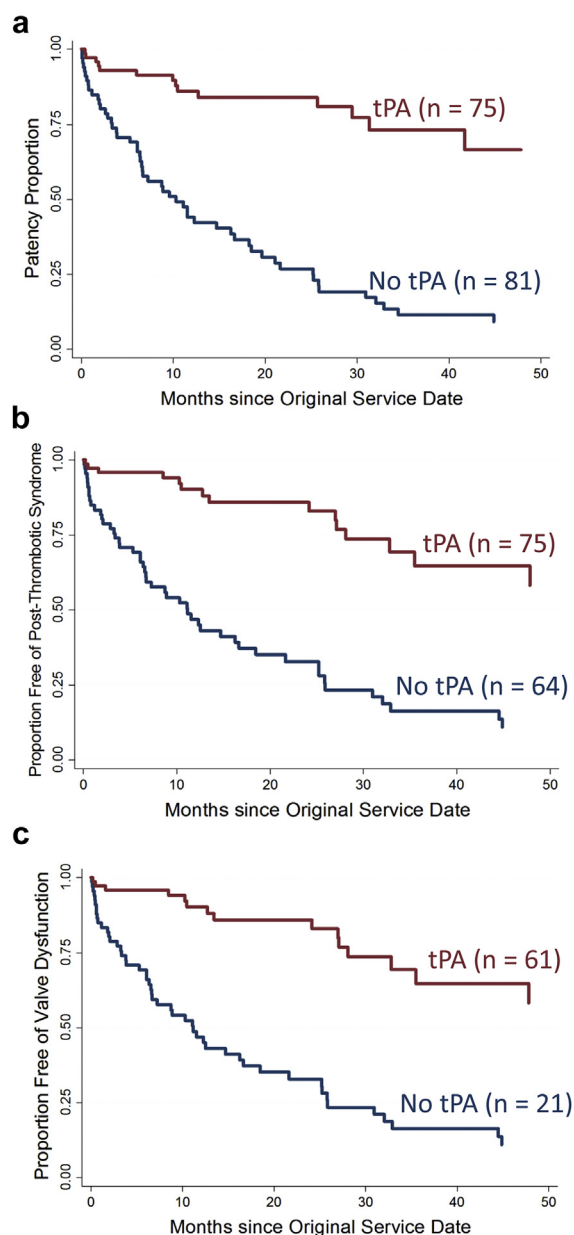
PTS, Post-thrombotic syndrome; tPA, tissue plasminogen activator.

was the only predictor of PTS from the model selection, and there was >90% (95% CI, 0.05-0.22;  $P < .001$ ) reduction of odds to have PTS for the patients who received tPA. Finally, the model selection found that immobility and tPA use were the predictors of valve dysfunction, and there was >90% (95% CI, 0.01-0.28;  $P < .001$ ) reduction of odds to have a valve dysfunction for the treatment group. The survival curves for patency (Fig 3, a), PTS (Fig 3, b), and valve dysfunction (Fig 3, c) clearly show the superiority of tPA use with regard to each factor being examined.

Of the three secondary outcomes examined in this study, there were no significant differences in the incidence of PE (34.1% vs 30.4%;  $P = .641$ ) and in-hospital mortality (0.0% vs 2.0%;  $P = .500$ ) between the treatment and control groups (Table III). However, there were significantly more patients with bleeding complications in the control group who received standard anticoagulation (14.7% vs 5.6%;  $P = .018$ ) compared with patients who received CDT. Multivariate logistic regression with model selection was performed on bleeding complications. Age was the only factor predictive for risk of bleeding, with a 5% (95% CI, 1.02-1.08;  $P = .004$ ) increase in odds of having a bleeding complication with each additional year of age.

## DISCUSSION

The exact role of CDT in the current management of lower extremity DVT remains undefined at this time. The upcoming Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial is the first multicenter randomized controlled trial to evaluate patients with both iliofemoral and femoral-popliteal DVT and may provide direction regarding the routine use of CDT in patients with lower extremity DVT.<sup>24</sup> In this retrospective cohort study, we found that CDT was associated with superior patency of the femoral-popliteal venous segment at 3 months and a resultant decrease in valvular dysfunction and PTS. These results were achieved without increased risk of bleeding compared with standard anticoagulation alone. Based on these results, we recommend the use of CDT for selected patients with a first episode of DVT who are younger with fewer medical comorbidities, who are more likely to have either a positive family history of



**Fig 3.** Survival curves for the three primary outcomes. **(a)** Proportion of patients who remained patent, **(b)** proportion of patients who remained free of post-thrombotic syndrome (PTS), and **(c)** proportion of patients who remained free of valvular dysfunction for the tissue plasminogen activator (tPA) vs no tPA group during the 48-month follow-up period. The red line represents patients who received tPA treatment, and the blue line represents patients who did not receive tPA treatment. Total number of patients from each group used in the survival analysis is shown.

thrombophilia or a positive hypercoagulable workup. This recommendation is consistent with previous studies that have suggested that CDT leads to a significant reduction in PTS and improvement in venous function.<sup>17,19,25-27</sup>

However, the widespread adoption of CDT has been limited by safety concerns, specifically the risk of bleeding (

complications. In the Catheter-directed Venous Thrombolysis (CaVenT) trial, the largest randomized controlled trial to date looking at additional CDT vs anticoagulation alone, 209 patients with acute iliofemoral DVT were assigned to treatment with additional CDT compared with conventional treatment alone. When bleeding events without clinical relevance were excluded, the CaVenT trial reported 20 cases of major bleeding related to CDT, a 9.5% bleeding complication rate.<sup>19</sup>

Our study differed from the CaVenT trial in that we restricted the use of tPA to <72 hours in duration, whereas the CaVenT trial patients were allowed up to 96 hours of lysis. Several studies have shown that longer duration of CDT is associated with adverse bleeding events.<sup>28,29</sup> In the CaVenT trial, the dose of alteplase was monitored and adjusted to keep activated partial thromboplastin time at 1.2 to 1.7 times higher than the upper normal limit, whereas alteplase dosage was monitored at our institution by fibrinogen levels. The control group (anticoagulation alone) in the CaVenT trial had no bleeding complications, making the bleeding events in the CDT group seemingly even more significant. This likely was a result of the highly selected good-risk patients who were enrolled in this study.

Two other recent studies have suggested increased risk of bleeding complications when instituting CDT: a 2014 Cochrane review, which combined several controlled trials that represented a cohort of 1103 patients; and a 2014 review of the National Inpatient Sample, which had a population of 7188 propensity score-matched patients.<sup>19,20</sup> These studies were pooled data from multiple institutions with potential variation in CDT protocols and patient selection criteria, which can greatly affect the risk of bleeding. Reported bleeding rates for anticoagulation range from 12% to 48%, and our results of 15% for the standard anticoagulation group certainly fall within that range.<sup>30</sup> We had a mixed group of patients, with patients in our anticoagulation group being sicker and having more comorbidities (eg, cancer and immobility). Previous literature has found age as a risk factor for bleeding with anticoagulation, and this was confirmed in our study as the multivariate analysis identified age as the sole predictive factor.<sup>31</sup> Our study was a single-center experience evaluating a specific protocol and patient selection criteria.

Although our study sought to examine patients with DVT affecting the femoral-popliteal segment, the majority of our study cohort had concurrent involvement of the iliofemoral segment seen on venography. Ultrasound as an imaging modality is highly dependent on multiple factors, including operator technique and the patient's habitus (obesity).

The limitations of our study include the retrospective design, which did not allow the control of patient variables. Patients selected for CDT were at low bleeding risk, and those denied CDT received anticoagulation. Despite this,

**Table III.** Secondary outcomes

	tPA (n = 89), No. (%)	Standard anticoagulation alone (n = 102), No. (%)	P value
Bleeding complications	5 (6)	15 (15)	.018
In-hospital mortality	0 (0)	2 (2)	.500
PE	30 (34)	31 (30)	.641

PE, Pulmonary embolism; tPA, tissue plasminogen activator.

Multivariate analysis identified age rather than the type of treatment rendered as predictive for risk of bleeding. Because of the small sample size, we were unable to identify a specific age limit beyond which we would not recommend CDT. Another limitation of our study was the short follow-up time of 3 months for the determination of primary outcomes. A longer study follow-up period would improve the strength of the findings.

Our patient cohort also represented the most severe and extensive lower extremity DVTs seen at our institution. It is unknown if CDT would have different outcomes in patients with less severe, partial DVT involving the femoral-popliteal segment. Finally, we did not stratify the severity of PTS on the basis of a scoring system. Therefore, it is unknown if CDT resulted in improvement in the grade of PTS compared with anticoagulation alone. Future studies should evaluate the role of CDT on the basis of severity and extent of DVT and look at potential beneficial outcomes based on grade of PTS.

## CONCLUSIONS

The results of our single-center study suggest that CDT is superior to standard anticoagulation alone in restoring patency to the femoral-popliteal venous segment in lower extremity DVT that was associated with proximal extension. Patients who received CDT also had lower incidence of PTS and less valve dysfunction. This was achieved without an increased risk of bleeding associated with the use of tPA compared with anticoagulation alone. Age was the major factor predicting risk of bleeding in either group. The results of this study may not be applicable to patients with pure femoral-popliteal venous segment DVT because only 3% of patients had this finding.

## AUTHOR CONTRIBUTIONS

Conception and design: ML, JH, MH, AM, DC

Analysis and interpretation: ML, JH, DC

Data collection: ML, MH

Writing the article: ML, JH, AM, DC

Critical revision of the article: ML, JH, MH, AM, DC

Final approval of the article: ML, JH, MH, AM, DC

Statistical analysis: JH

Obtained funding: Not applicable

Overall responsibility: DC

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