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Recommended Citation

Vedantham, S.; Lewis, L.; Duncan, J. R.; Nieters, P. Washington University School of Medicine in St. Louis; Derfler, M. C.; Saad, N.; Blinder, M.; and et al, "Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis." *The New England Journal of Medicine*. 377, 23. 2240-2252. (2017).
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ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

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ABSTRACT

BACKGROUND

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Vedantham at Washington University in St. Louis, Mallinckrodt Institute of Radiology, 510 S. Kingshighway Blvd., St. Louis, MO 63110, or at vedanthams@wustl.edu.

The post-thrombotic syndrome frequently develops in patients with proximal deep-vein thrombosis despite treatment with anticoagulant therapy. Pharmacomechanical catheter-directed thrombolysis (hereafter “pharmacomechanical thrombolysis”) rapidly removes thrombus and is hypothesized to reduce the risk of the post-thrombotic syndrome.

METHODS

*A complete list of investigators in the ATTRACT trial is provided in the Supplementary Appendix, available at NEJM.org.

We randomly assigned 692 patients with acute proximal deep-vein thrombosis to receive either anticoagulation alone (control group) or anticoagulation plus pharmacomechanical thrombolysis (catheter-mediated or device-mediated intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting). The primary outcome was development of the post-thrombotic syndrome between 6 and 24 months of follow-up.

This article was updated on December 7, 2017, at NEJM.org.

N Engl J Med 2017;377:2240-52.
DOI: 10.1056/NEJMoa1615066

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RESULTS

Between 6 and 24 months, there was no significant between-group difference in the percentage of patients with the post-thrombotic syndrome (47% in the pharmacomechanical-thrombolysis group and 48% in the control group; risk ratio, 0.96; 95% confidence interval [CI], 0.82 to 1.11; $P=0.56$). Pharmacomechanical thrombolysis led to more major bleeding events within 10 days (1.7% vs. 0.3% of patients, $P=0.049$), but no significant difference in recurrent venous thromboembolism was seen over the 24-month follow-up period (12% in the pharmacomechanical-thrombolysis group and 8% in the control group, $P=0.09$). Moderate-to-severe post-thrombotic syndrome occurred in 18% of patients in the pharmacomechanical-thrombolysis group versus 24% of those in the control group (risk ratio, 0.73; 95% CI, 0.54 to 0.98; $P=0.04$). Severity scores for the post-thrombotic syndrome were lower in the pharmacomechanical-thrombolysis group than in the control group at 6, 12, 18, and 24 months of follow-up ($P<0.01$ for the comparison of the Villalta scores at each time point), but the improvement in quality of life from baseline to 24 months did not differ significantly between the treatment groups.

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute and others; ATTRACT ClinicalTrials.gov number, NCT00790335.)

DESPITE THE USE OF ANTICOAGULANT therapy, the post-thrombotic syndrome develops within 2 years in approximately half of patients with proximal deep-vein thrombosis.¹⁻⁴ The post-thrombotic syndrome commonly causes chronic limb pain and swelling and can progress to cause major disability, leg ulcers, and impaired quality of life.^{5,6} Small randomized trials have suggested that active removal of acute thrombus may preserve venous function and prevent the post-thrombotic syndrome (the “open-vein hypothesis”).^{3,7,8}

Pharmacomechanical catheter-directed thrombolysis (hereafter “pharmacomechanical thrombolysis”) is the delivery of a fibrinolytic drug into the thrombus with concomitant thrombus aspiration or maceration.⁹ The objective of pharmacomechanical thrombolysis is to diminish the thrombus burden by means of low-dose fibrinolysis and mechanical therapy, thereby reducing the risk of the post-thrombotic syndrome while minimizing the risk of bleeding.¹⁰⁻¹³ We performed the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial to determine whether pharmacomechanical thrombolysis prevents the post-thrombotic syndrome in patients with proximal deep-vein thrombosis.

METHODS

TRIAL ORGANIZATION

We conducted a phase 3, multicenter, randomized, open-label, assessor-blinded, controlled clinical trial sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Boston Scientific and Covidien (now Medtronic) provided supplemental funding. The trial drug and additional funding were provided by Genentech. Compression stockings were donated by BSN Medical. These companies played no role in the design or conduct of the trial or in the analysis or reporting of the data.

The trial was approved by the institutional review boards at all participating centers. The steering committee and site investigators were responsible for the design¹⁴ and conduct of the trial, respectively. The contract research organization Inclinix provided guidance to support participant-recruitment efforts, and data analyses were conducted by the trial statistical staff (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The

steering committee vouches for the accuracy and completeness of the data and the analyses and for the fidelity of the trial to the protocol, which is available at NEJM.org.

PATIENT POPULATION

Patients with symptomatic proximal deep-vein thrombosis involving the femoral, common femoral, or iliac vein (with or without other involved ipsilateral veins) were enrolled at 56 clinical centers in the United States. Patients were excluded if they were younger than 16 or older than 75 years of age, were pregnant, had had symptoms for more than 14 days, were at high bleeding risk, had active cancer, had established post-thrombotic syndrome, or had had ipsilateral deep-vein thrombosis in the previous 2 years. The full list of eligibility criteria, investigators, and sites is provided in the Supplementary Appendix. All the patients provided written informed consent.

RANDOMIZATION

Patients were randomly assigned in a 1:1 ratio to the pharmacomechanical-thrombolysis group or the control group (no procedural intervention) with the use of a Web-based central randomization system that ensured concealment of the treatment assignments. Randomization was stratified according to clinical center and thrombus extent (i.e., whether thrombosis involved the common femoral or iliac vein [iliofemoral deep-vein thrombosis] or not [femoropopliteal deep-vein thrombosis]). The randomization sequence, with varying block sizes, was computer-generated by an independent statistician.

TREATMENT AND OUTCOME ASSESSMENTS

Patients in each treatment group received initial and long-term anticoagulant therapy consistent with published guidelines, including the option of rivaroxaban when it became available, and were provided sized-to-fit, knee-high, elastic compression stockings providing 30 to 40 mm Hg of pressure (BSN Medical) at the 10-day follow-up visit and every 6 months.^{15,16} Pharmacomechanical catheter-directed thrombolysis was performed in a manner consistent with published guidelines by board-certified physicians whose credentials were approved by the trial leadership.^{14,17,18} A detailed description of these methods is provided in the Supplementary Appendix.

Recombinant tissue plasminogen activator (rt-PA) (alteplase [Activase, Genentech] at a dose

of <35 mg) was delivered into the thrombus by one of three methods. If the popliteal vein was occluded or the inferior vena cava was involved, physicians were required to use “infusion-first” therapy, which started with rt-PA infusion through a multi-sidehole catheter of the physician’s choice for no longer than 30 hours. For the remaining patients, physicians were required to first attempt single-session thrombus removal with rapid delivery of rt-PA through the AngioJet Rheolytic Thrombectomy System (Boston Scientific) or the Trellis Peripheral Infusion System (Covidien) and then to infuse rt-PA for no longer than 24 hours if residual thrombus was present.

After the initial delivery of rt-PA, physicians could use balloon maceration, catheter aspiration, thrombectomy with the use of the AngioJet or Trellis system, percutaneous transluminal balloon venoplasty, stent placement (iliac or common femoral vein), or a combination of procedures to clear residual thrombus and treat obstructive lesions.^{17,18} Stenting was encouraged for lesions that were causing 50% or greater narrowing of the diameter of the vein, robust collateral filling, or a mean pressure gradient of more than 2 mm Hg. Treatment was discontinued when there was at least 90% thrombus removal with restoration of flow or when there was a serious complication.

The international normalized ratio was required to be 1.6 or lower at the start of pharmacomechanical thrombolysis. During the procedure, patients received twice-daily subcutaneous injections of low-molecular-weight heparin in therapeutic doses or unfractionated heparin infusions (with the dose reduced to 6 to 12 units per kilogram of body weight per hour [maximum, 1000 units per hour] during rt-PA infusions). Additional unfractionated heparin boluses (up to 50 units per kilogram) were given during the procedure at the physician’s discretion.

Trial outcomes were assessed at 10 and 30 days and 6, 12, 18, and 24 months after randomization. The clinical personnel who performed assessments of efficacy outcomes and the adjudicators of safety and efficacy outcomes were unaware of the treatment assignments.

PRIMARY EFFICACY OUTCOME

Development of the post-thrombotic syndrome, the primary efficacy outcome, was defined as a Villalta score of 5 or higher or an ulcer in the leg with the index deep-vein thrombosis, at any time

between the 6-month follow-up visit and the 24-month follow-up visit.^{19,20} The Villalta scale ranges from 0 to 33, with higher scores indicating more severe post-thrombotic syndrome (details are provided in the Supplementary Appendix). Patients were also counted as having the post-thrombotic syndrome if they underwent an unplanned endovascular procedure to treat severe venous symptoms beyond 6 months after randomization, unless a Villalta score within the previous 4 weeks was lower than 5.

SECONDARY EFFICACY AND SAFETY OUTCOMES

The occurrence of the post-thrombotic syndrome at 6, 12, 18, and 24 months was counted if the Villalta score at that visit was 5 or higher. The severity of the post-thrombotic syndrome was evaluated at 6, 12, 18 and 24 months with the use of the Villalta scale and the Venous Clinical Severity Score²¹ (scores range from 0 to 27, with higher scores indicating more severe post-thrombotic syndrome). The proportion of patients with moderate-to-severe post-thrombotic syndrome (Villalta score, ≥ 10) was also assessed.

A major non-post-thrombotic syndrome treatment failure was assessed when any of three events occurred in the index leg: an unplanned endovascular procedure to treat severe venous symptoms within 6 months, venous gangrene within 6 months, or an amputation within 24 months. The combined outcome of the post-thrombotic syndrome or major non-post-thrombotic syndrome treatment failure was also assessed.

Patient-reported health-related quality of life at baseline and 24 months was assessed with the use of the generic Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)²² and the venous disease-specific Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) measure.²³ Leg pain and leg swelling at baseline, 10 days, and 30 days were assessed with the use of a 7-point Likert pain scale (with higher scores indicating more severe pain)²⁴ and by measuring calf circumference, respectively.

In the pharmacomechanical-thrombolysis group, thrombus removal was quantified by independent central readers who scored venograms obtained before and after the procedure, using the proximal-vein components of the Marder score.²⁵ The modified Marder score ranges from

0 to 24, with 0 representing no thrombus and 24 representing complete thrombosis.

Safety outcomes included bleeding, recurrent venous thromboembolism, and death, which were reported throughout follow-up and summarized through 10 days and 24 months.²⁶ A detailed description of all trial outcomes is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that the post-thrombotic syndrome would develop in 30% of the patients in the control group between 6 and 24 months^{1,27-29} and hypothesized that pharmacomechanical thrombolysis would reduce this percentage to 20% or lower.³⁰⁻³³ Assuming a 10% loss to follow-up, we calculated that 692 patients would be required in order for the trial to have 80% power to detect the hypothesized treatment effect at a two-sided α of 0.05.

Two types of analyses were performed: a modified intention-to-treat analysis that included all patients who underwent randomization except those who did not have deep-vein thrombosis at enrollment, and a per-protocol analysis that excluded patients who, within 7 days after randomization, were randomly assigned to receive pharmacomechanical thrombolysis but did not receive it or who were randomly assigned to the control group but had skin puncture for pharmacomechanical thrombolysis or any thrombolytic therapy.

The primary analysis was a modified intention-to-treat analysis that compared the cumulative proportion of patients who had development of the post-thrombotic syndrome within 24 months between the treatment groups with the use of the Cochran–Mantel–Haenszel test with adjustment for the two stratification variables. A two-sided P value of 0.05 or lower was considered to indicate statistical significance. The treatment effects are summarized with the use of stratum-adjusted risk ratios and their corresponding 95% confidence intervals. To account for the missing assessments during follow-up, a sensitivity analysis with multiple imputation, under the assumption that data were missing at random, was conducted on the Cochran–Mantel–Haenszel risk-ratio estimates with the use of prespecified auxiliary variables (age, sex, body-mass index, extent of deep-vein thrombosis, the maximum Villalta score observed at assessments from 6 to 24 months, and available Villalta scores at baseline, 10 days,

or 30 days). Details are provided in the Supplementary Appendix.

Prespecified secondary analyses included a per-protocol analysis of the primary outcome and modified intention-to-treat and per-protocol analyses of each of the secondary efficacy outcomes. Stratum-adjusted Cochran–Mantel–Haenszel tests were used for the analysis of each of the categorical secondary outcomes and safety outcomes. The mean Villalta and Venous Clinical Severity Score assessments at each visit were estimated with the use of piecewise linear-regression growth-curve models with adjustment for strata and prespecified baseline covariates (age, sex, body-mass index, and Villalta score). Changes from baseline to 24 months in quality-of-life scores and from baseline to 10 and 30 days in leg-pain scores and calf circumferences were compared between the two treatment groups by means of linear regression with adjustment for strata. To account for multiple testing, a two-sided P value of 0.01 or lower was considered to indicate statistical significance for the secondary efficacy analyses. A two-sided P value of 0.05 or lower was considered to indicate statistical significance for the safety analyses.

RESULTS

CHARACTERISTICS OF THE PATIENTS AT BASELINE

From December 2009 through December 2014, a total of 692 patients underwent randomization (337 to the pharmacomechanical-thrombolysis group and 355 to the control group) (Fig. 1). One patient who was assigned to the pharmacomechanical-thrombolysis group was excluded from all analyses; on review of prerandomization assessments by personnel who were unaware of the treatment assignments, this patient was found not to have a qualifying deep-vein thrombosis. The baseline characteristics of the patients were similar in the treatment groups (Table 1, and Table S2 in the Supplementary Appendix).

PROTOCOL AND TREATMENT ADHERENCE

Within 7 days after randomization, 5 patients who had been assigned to the control group underwent pharmacomechanical thrombolysis, and 11 patients who had been assigned to the pharmacomechanical-thrombolysis group did not undergo the procedure. These patients were excluded from the per-protocol analysis. The use of anticoagula-

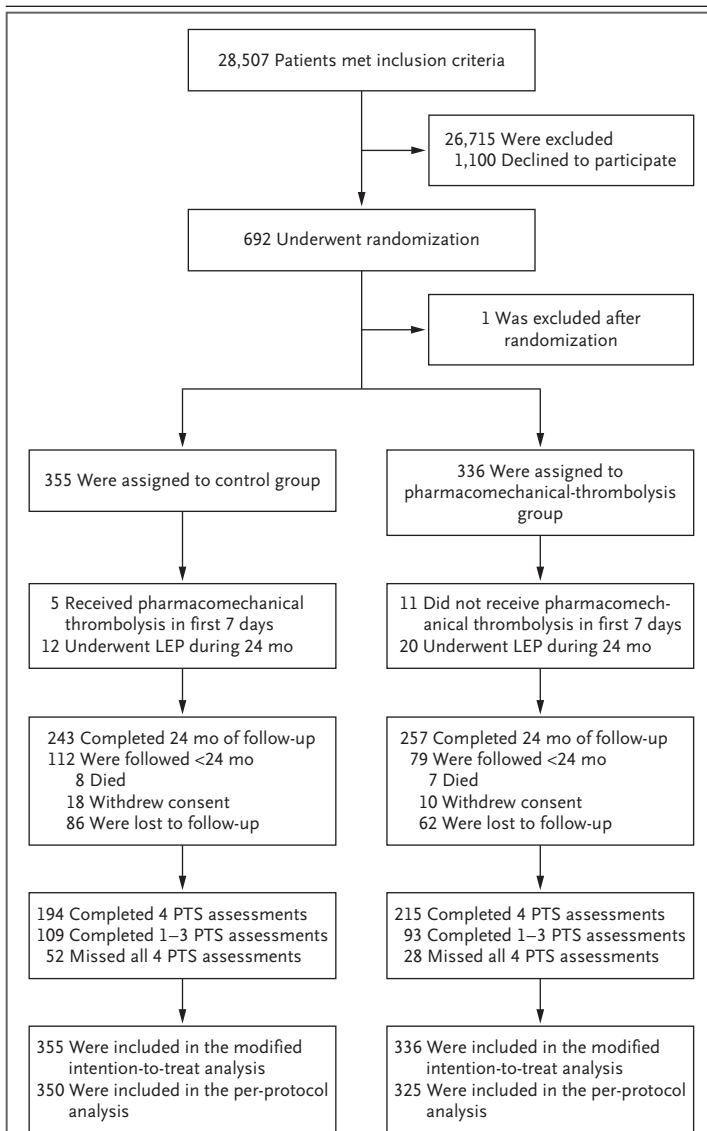


Figure 1. Enrollment, Randomization, and Follow-up.

The reasons for the exclusion of patients before randomization are shown in Table S1 in the Supplementary Appendix. Randomization was stratified according to clinical center and extent of deep-vein thrombosis. Two patients (one in each treatment group) missed all four assessments for the post-thrombotic syndrome (PTS) because they died before 6 months. LEP denotes late endovascular procedure.

tion and compression stockings and the elements of pharmacomechanical thrombolysis are summarized in Table 2. The mean duration of anticoagulation before the first permanent cessation was similar in the two treatment groups (median days to stopping, 211 days in the pharmacomechanical-thrombolysis group and 231 days in the control group; $P=0.16$) (Table 2). Pharmaco-

mechanical thrombolysis was performed at a median of 1 day after randomization. The mean degree of thrombus removal was 76% (mean pre-procedure Marder score, 11.4; mean post-procedure Marder score, 2.7; change, -8.7 ; 95% confidence interval [CI], -8.1 to -9.4 ; $P<0.001$).

POST-THROMBOTIC SYNDROME

In the primary analysis, the post-thrombotic syndrome developed over the 24-month period in 157 of 336 patients (47%) assigned to the pharmacomechanical-thrombolysis group and in 171 of 355 patients (48%) assigned to the control group (risk ratio, 0.96; 95% CI, 0.82 to 1.11; $P=0.56$) (Table 3). The findings were similar in a per-protocol analysis (151 of 325 patients who underwent pharmacomechanical thrombolysis and 169 of 350 who did not undergo pharmacomechanical thrombolysis; risk ratio, 0.94; 95% CI, 0.81 to 1.10) and in a sensitivity analysis with multiple imputation (risk ratio, 0.89; 95% CI, 0.78 to 1.02) (Tables S3 and S4 in the Supplementary Appendix). The results were similar in prespecified subgroups (Fig. S1 in the Supplementary Appendix), except for a suggestion that patients 65 years of age or older were less likely to benefit from pharmacomechanical thrombolysis than younger patients ($P=0.04$ for the interaction).

SECONDARY EFFICACY OUTCOMES

There was no significant between-group difference in the percentage of patients who had major non-post-thrombotic syndrome treatment failure or overall treatment failure ($P\leq 0.01$ was considered to indicate statistical significance for the secondary efficacy analyses) (Table 3). Moderate-to-severe post-thrombotic syndrome (Villalta score, ≥ 10) occurred in 18% of the patients in the pharmacomechanical thrombolysis group and 24% of those in the control group (risk ratio, 0.73; 95% CI, 0.54 to 0.98; $P=0.04$). The severity of the post-thrombotic syndrome, as assessed by the mean Villalta score and mean Venous Clinical Severity Score, was significantly lower in the pharmacomechanical-thrombolysis group than in the control group at all visits between 6 and 24 months ($P\leq 0.01$ for the between-group comparison at each time point, with the exception of the comparison of the Venous Clinical Severity Score at 24 months, for which $P=0.03$) (Table 4). Over the 24-month period, there was no signifi-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pharmacomechanical-Thrombolysis Group (N=336)	Control Group (N=355)	Total (N=691)
Median age (IQR) — yr	52 (41–62)	53 (43–62)	53 (42–62)
Male sex — no. (%)	205 (61)	221 (62)	426 (62)
Race — no. (%)†			
White	265 (79)	276 (78)	541 (78)
Black	61 (18)	62 (17)	123 (18)
Other	10 (3)	17 (5)	27 (4)
Median weight (IQR) — kg	95 (81–111)	92 (79–110)	93 (80–110)
Median body-mass index (IQR)‡	31 (27–36)	30 (26–35)	31 (27–35)
Villalta score — no. (%)§			
0–4	57 (17)	69 (19)	126 (18)
5–9	115 (34)	124 (35)	239 (35)
10–14	98 (29)	94 (26)	192 (28)
≥15	66 (20)	66 (19)	132 (19)
Index deep-vein thrombosis in left leg — no. (%)	207 (62)	218 (61)	425 (62)
Deep-vein thrombosis extends into common femoral vein, iliac vein, or both — no. (%)	195 (58)	196 (55)	391 (57)
Previous deep-vein thrombosis or pulmonary embolism — no. (%)	83 (25)	87 (25)	170 (25)
Previous ipsilateral deep-vein thrombosis — no. (%)	5 (1)	14 (4)	19 (3)
Deep-vein thrombosis risk factors — no. (%)¶			
Major surgery	27 (8)	34 (10)	61 (9)
Hospitalization	26 (8)	38 (11)	64 (9)
Plaster cast immobilization	8 (2)	9 (3)	17 (2)
Childbirth	3 (1)	5 (1)	8 (1)
Outpatient — no. (%)	268 (80)	300 (85)	568 (82)
Median interval from start of symptoms of deep-vein thrombosis to randomization (IQR) — days	6 (4–10)	6 (4–9)	6 (4–10)
Aspirin use within 7 days before randomization — no. (%)	68 (20)	74 (21)	142 (21)
Median estimated glomerular filtration rate (IQR) — ml/min	86 (70–102)	86 (71–102)	86 (71–102)
Prerandomization anticoagulant therapy — no. (%)¶¶	314 (93)	331 (93)	645 (93)
Low-molecular-weight heparin	180 (57)	205 (62)	385 (60)
Unfractionated heparin	99 (32)	99 (30)	198 (31)
Rivaroxaban	16 (5)	11 (4)	27 (4)
Other	18 (5)	16 (5)	34 (5)
Warfarin	154 (49)	179 (57)	333 (52)

* IQR denotes interquartile range.

† Race was reported by the patient.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The Villalta scale is an assessment of five patient-reported symptoms (cramps, itching, pins and needles, leg heaviness, and pain) and six signs reported by clinicians who were unaware of the treatment assignments (pretibial edema, skin induration, hyperpigmentation, venous ectasia, redness, and pain during calf compression), scored on a 4-point scale (a score of 0 denotes none or minimal, 1 mild, 2 moderate, and 3 severe) and summed into a total score for each leg; a leg with an ulcer was assigned a minimum score of 15 points. Total scores range from 0 to 33, with higher scores indicating more severe post-thrombotic syndrome; a score of 0 to 4 denotes none or minimal, 5 to 9 mild, 10 to 14 moderate, and 15 or higher severe. Two patients in the control group were not assessed.

¶ Patients could be included in more than one category.

¶¶ Anticoagulant therapy that was given after the diagnosis of deep-vein thrombosis and before randomization is shown.

Table 2. Treatment after Randomization.*

Treatment	Pharmacomechanical-Thrombolysis Group (N=336)	Control Group (N=355)
Initial anticoagulant therapy — no./total no. (%) †‡		
Unfractionated heparin	118/334 (35)	69/352 (20)
Low-molecular-weight heparin	181/334 (54)	227/352 (64)
Other	49/334 (15)	71/352 (20)
Therapy at 30 days — no./total no. (%) ‡		
Any anticoagulant therapy	314/321 (98)	316/322 (98)
Antiplatelet therapy	47/321 (15)	43/322 (13)
Compression stockings used ≥3 days/wk	252/321 (79)	252/322 (78)
Therapy at 6 mo — no./total no. (%) ‡		
Any anticoagulant therapy	227/290 (78)	247/286 (86)
Antiplatelet therapy	60/290 (21)	38/286 (13)
Compression stockings used ≥3 days/wk	192/290 (66)	197/286 (69)
Therapy at 24 mo — no./total no. (%) ‡		
Any anticoagulant therapy	120/251 (48)	117/236 (50)
Antiplatelet therapy	71/251 (28)	62/236 (26)
Compression stockings used ≥3 days/wk	138/251 (55)	130/236 (55)
Duration of anticoagulant therapy		
Never started — no. (%)	2 (1)	3 (1)
Not stopped during trial period — no. (%)	185 (55)	203 (57)
Stopped during trial period — no. (%)	149 (44)	149 (42)
Median days to stopping (IQR)	211 (179–360)	231 (189–371)
Details of pharmacomechanical thrombolysis		
Initial rt-PA delivery method		
Infusion-first — no. (%)	194 (58)	—
Median rt-PA total dose (IQR) — mg	21 (18–26)	—
rt-PA duration — hr§	22±6.5	—
% with duration <4 hr	0	—
AngioJet — no. (%)	75 (22)	—
Median rt-PA total dose (IQR) — mg	21 (12–28)	—
rt-PA duration — hr§	20±5.3	—
% with duration <4 hr	45	—
Trellis — no. (%)	50 (15)	—
Median rt-PA total dose (IQR) — mg	20 (12–25)	—
rt-PA duration — hr§	19±5.7	—
% with duration <4 hr	62	—
Other — no. (%)¶	17 (5)	—
Additional endovascular methods used — no. (%)		
None	39 (12)	—
1 or more	297 (88)	—

Table 2. (Continued.)

Treatment	Pharmacomechanical-Thrombolysis Group (N=336)	Control Group (N=355)
Type of additional method — no./total no. (%)‡		
Balloon venoplasty	184/297 (62)	—
Balloon maceration	183/297 (62)	—
Rheolytic thrombectomy with AngioJet	180/297 (61)	—
Stent placement	82/297 (28)	—
Large-bore catheter aspiration	63/297 (21)	—
Isolated thrombolysis with Trellis	14/297 (5)	—
Type of stent placed — no./total no. (%)‡		
Wallstent (Boston Scientific)	34/82 (41)	—
SMART (Cordis)	12/82 (15)	—
Protégé (Covidien [now Medtronic])	10/82 (12)	—
Zilver (Cook Medical)	6/82 (7)	—
Luminexx (C.R. Bard)	5/82 (6)	—
Lifestar (C.R. Bard)	2/82 (2)	—
EPIC (Boston Scientific)	2/82 (2)	—
Viabahn (Gore)	1/82 (1)	—
Multiple types	7/82 (9)	—
Not specified	3/82 (4)	—

* Plus-minus values are means \pm SD. The abbreviation rt-PA denotes recombinant tissue plasminogen activator.

† Anticoagulant therapy given after randomization is shown.

‡ Patients could be included in more than one category.

§ Distributions are bimodal, with spikes below 4 hours (means and standard deviations are for data after 4 hours).

¶ Other includes 10 procedures in which there was no acute thrombus found on venogram and 7 that were not attempted.

cant between-group difference in the change in venous disease-specific quality of life ($P=0.08$) or general quality of life ($P=0.37$). The mean decreases in leg pain from baseline in the pharmacomechanical-thrombolysis group and the control group were 1.62 and 1.29 Likert points at 10 days, respectively ($P=0.02$), and 2.17 and 1.83 Likert points at 30 days, respectively ($P=0.03$). For leg circumference, a decrease of 0.26 cm and an increase of 0.27 cm from baseline at 10 days occurred in the pharmacomechanical-thrombolysis group and the control group, respectively ($P=0.02$), and decreases from baseline of 0.74 cm and 0.28 cm had occurred at 30 days, respectively ($P=0.05$). The results of the per-protocol analyses were similar to those of the modified intention-to-treat analyses (Tables S5 and S6 in the Supplementary Appendix).

SAFETY OUTCOMES

Major bleeding within 10 days occurred in 6 patients (1.7%) assigned to the pharmacomechanical-thrombolysis group, as compared with 1 patient (0.3%) assigned to the control group ($P=0.049$) (Table 3). Details of the bleeding events are shown in Table S7 in the Supplementary Appendix. Recurrent venous thromboembolism within 24 months occurred in 42 patients (12%) assigned to the pharmacomechanical-thrombolysis group (including 1 fatal pulmonary embolism at 6 months) and in 30 patients (8%) assigned to the control group ($P=0.09$). Of the 15 deaths that occurred (7 in the pharmacomechanical thrombolysis group and 8 in the control group), none occurred within 10 days after randomization (Table 3, and Table S8 in the Supplementary Appendix).

Table 3. Binary Trial Outcomes.

Outcome	Pharmacomechanical- Thrombolysis Group (N=336) <i>number of patients (percent)</i>	Control Group (N=355) <i>number of patients (percent)</i>	Risk Ratio (95% CI)	P Value
Post-thrombotic syndrome between 6 and 24 mo*				
Ulcer at any follow-up assessment	12 (4)	17 (5)		
Villalta score ≥ 5 without ulcer	144 (43)	154 (43)		
Late endovascular procedure only	1 (<1)	0		
Total	157 (47)	171 (48)	0.96 (0.82–1.11)†	0.56
Post-thrombotic syndrome according to follow-up visit‡				
At 6 mo	78/291 (27)	113/285 (40)	0.68 (0.53–0.86)	
At 12 mo	92/272 (34)	88/258 (34)	0.99 (0.78–1.26)	
At 18 mo	85/245 (35)	76/222 (34)	1.01 (0.79–1.30)	
At 24 mo	79/258 (31)	86/239 (36)	0.85 (0.66–1.09)	
Major non–post-thrombotic syndrome treatment failure	4 (1)	7 (2)	0.58 (0.17–1.98)§	0.38¶
Any treatment failure	158 (47)	176 (50)	0.94 (0.80–1.09)†	0.39¶
Moderate-to-severe post-thrombotic syndrome**	60 (18)	84 (24)	0.73 (0.54–0.98)†	0.04¶
Major bleeding††				
First 10 days	6 (1.7)	1 (0.3)	6.18 (0.78–49.2)§	0.049
Total over 24 mo	19 (5.7)	13 (3.7)	1.52 (0.76–3.01)§	0.23
Any bleeding				
First 10 days	15 (4)	6 (2)	2.64 (1.04–6.68)§	0.03
Total over 24 mo	46 (14)	38 (11)	1.26 (0.85–1.89)§	0.25
Recurrent venous thromboembolism				
First 10 days	6 (2)	4 (1)	1.53 (0.44–5.28)§	0.50
Total over 24 mo	42 (12)	30 (8)	1.47 (0.94–2.29)§	0.09
Death				
First 10 days	0	0		
Total over 24 mo	7 (2)	8 (2)	0.89 (0.33–2.44)	0.83

* Data are the cumulative percentage of patients in whom the post-thrombotic syndrome (ulcer, Villalta score ≥ 5 , or late endovascular procedure) developed at any time from 6 through 24 months.

† The estimate is from a Cochran–Mantel–Haenszel test with adjustment for the extent of deep-vein thrombosis and clinical center.

‡ Data are the percentage of patients at each visit with any post-thrombotic syndrome according to the Villalta scale among those who had an assessment performed (denominator).

§ The estimate is from a Cochran–Mantel–Haenszel test with adjustment for the extent of deep-vein thrombosis.

¶ For the secondary efficacy analyses, a P value of 0.01 or lower was considered to indicate statistical significance.

|| Data are for a composite of post-thrombotic syndrome or major non–post-thrombotic syndrome treatment failure.

** Data are the cumulative percentage of patients with moderate or severe post-thrombotic syndrome (prespecified analysis), defined as a Villalta score of 10 or higher.

†† More precise percentages are provided for major bleeding to show the magnitude of the between-group difference in risk.

DISCUSSION

In this trial, pharmacomechanical thrombolysis did not prevent the post-thrombotic syndrome in patients with acute proximal deep-vein thrombosis; this finding persisted in per-protocol

analyses and was consistent across all prespecified subgroups. In the pharmacomechanical-thrombolysis group, there were more early major bleeds than in the control group, but less major bleeding (1.7% of patients, with no fatal or intracranial bleeds) occurred in association with the

Table 4. Continuous Trial Outcomes.

Outcome	Pharmacomechanical-Thrombolysis Group (N=336)		Control Group (N=355)		Between-Group Difference	
	No. of Patients	Mean ±SE	No. of Patients	Mean ±SE	Estimate ±SE	P Value*
Villalta score†						
At 6 mo	291	3.11±0.24	285	4.33±0.24	-1.22±0.31	<0.001
At 12 mo	272	3.22±0.22	258	4.38±0.22	-1.17±0.28	<0.001
At 18 mo	245	3.32±0.24	222	4.44±0.24	-1.12±0.31	<0.001
At 24 mo	258	3.43±0.28	239	4.50±0.29	-1.06±0.38	0.005
VCSS score‡						
At 6 mo	289	1.73±0.15	279	2.68±0.15	-0.95±0.21	<0.001
At 12 mo	265	1.80±0.16	253	2.37±0.16	-0.56±0.23	0.01
At 18 mo	240	1.74±0.17	215	2.80±0.18	-1.06±0.24	<0.001
At 24 mo	235	1.87±0.18	214	2.42±0.19	-0.55±0.26	0.03
Change in SF-36 general quality of life§						
PCS, baseline to 24 mo	245	11.18±0.91	222	10.06±0.97	1.13±1.26	0.37
MCS, baseline to 24 mo	245	2.70±0.84	222	2.70±0.89	0.00±1.16	0.99
Change in VEINES disease-specific quality of life¶						
Overall, baseline to 24 mo	249	27.67±1.71	226	23.47±1.83	4.20±2.39	0.08
Symptoms, baseline to 24 mo	248	20.58±1.70	226	17.31±1.81	3.27±2.37	0.17
Change in leg-pain severity¶**						
Baseline to day 10	317	-1.62±0.10	325	-1.29±0.10	-0.33±0.14	0.02
Baseline to day 30	314	-2.17±0.11	317	-1.83±0.11	-0.34±0.15	0.03
Change in index-leg circumference — cm¶††						
Baseline to day 10	305	-0.26±0.17	323	0.27±0.16	-0.53±0.23	0.02
Baseline to day 30	304	-0.74±0.17	315	-0.28±0.16	-0.46±0.23	0.05

* For the secondary efficacy analyses, a P value of 0.01 or lower was considered to indicate statistical significance.

† Mean scores, standard errors, and between-group differences were estimated with the use of growth-curve models and piecewise linear regression with adjustment for the extent of deep-vein thrombosis and clinical center and for baseline covariates (age, sex, body-mass index, and Villalta score).

‡ The Venous Clinical Severity Score (VCSS) ranges from 0 to 27, with higher scores indicating more severe post-thrombotic syndrome.

§ The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) includes a physical component score (PCS) and a mental component score (MCS). Each score ranges from 0 to 100, with higher scores indicating better quality of life. A difference of 3 to 4 points is considered clinically meaningful.

¶ Mean changes in scores, standard errors, and between-group differences were estimated with the use of multiple linear regression with adjustment for the extent of deep-vein thrombosis and clinical center.

|| The Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) measure includes an overall score and a symptom-specific score. Each score ranges from 0 to 100, with higher scores indicating better quality of life. A difference of 3 to 4 points is considered clinically meaningful.

** The patient-reported severity of pain in the index leg was measured on a Likert scale. Scores range from 0 to 7, with higher scores indicating more severe pain.

†† Leg circumference was measured at 10 cm below the tibial tuberosity of the index leg.

procedure than in past studies of thrombolysis for deep-vein thrombosis.^{3,7,18,34-36}

In the recent CAVENT (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis) trial, catheter-directed thromboly-

sis reduced the risk of the post-thrombotic syndrome over periods of 2 and 5 years.^{3,34} Our trial, for uncertain reasons, did not confirm these findings. Differences between the two trials include the larger size of our trial (692 vs. 209

patients), its geographic and demographic scope (56 U.S. centers vs. 4 Norwegian centers), and our greater use of mechanical therapies versus the longer rt-PA infusions used in the CAVENT trial. Inadequate thrombus removal is unlikely to explain the failure of pharmacomechanical thrombolysis to prevent the post-thrombotic syndrome in our trial, since venography showed effective thrombus removal. Standard care for deep-vein thrombosis did not substantially differ between the two treatment groups and would not explain the observed lack of a beneficial effect of pharmacomechanical thrombolysis in preventing the post-thrombotic syndrome.

Our trial had several limitations. There was a substantial number of missing assessments of the post-thrombotic syndrome. As expected, there were occasional missed visits among patients who returned for follow-up, which were balanced between the treatment groups. However, among the 80 patients with no post-thrombotic syndrome assessments, two thirds were in the control group, which is likely to have resulted in an underestimate of the treatment effect. Although the sensitivity analysis conducted with the use of methods to impute assessments of the post-thrombotic syndrome in these patients yielded findings similar to those in the primary analysis, the extent of incomplete follow-up is still a limitation of the trial.

A large number of patients had to be screened in order to enroll our target sample; this largely reflects the exclusion of patients who would not receive pharmacomechanical thrombolysis in clinical practice (e.g., patients with a high bleeding risk), but it could reduce the generalizability of the trial. The trial was medium-sized, but given the risks of pharmacomechanical thrombolysis, it was unlikely to miss a treatment effect of sufficient size to influence clinical practice. However, the trial had limited power to examine treatment effects within subgroups. Although many elements of pharmacomechanical thrombolysis were standardized, there was variation in how the procedure was performed, in order to accommodate patient-specific differences and physician preferences. We did not randomly assign patients to specific treatment methods, which precluded a direct comparison of outcomes among the methods. Finally, most patients received warfarin; although direct oral anticoagulants are now frequently used, this change should not have

affected the rates of the post-thrombotic syndrome, since both types of anticoagulation are similarly effective at preventing recurrent deep-vein thrombosis.^{15,37}

Because the post-thrombotic syndrome varies in its clinical manifestations, we evaluated its presence and severity in complementary ways. Assessments made with the use of the Villalta scale and the Venous Clinical Severity Score were consistent in suggesting that pharmacomechanical thrombolysis reduced the severity of the post-thrombotic syndrome, which raises the possibility that the etiologic factors that predispose patients to the development of the post-thrombotic syndrome may differ at least partly from those that determine progression to advanced post-thrombotic syndrome. Further study of the open-vein hypothesis may help to define the pathophysiological basis of the post-thrombotic syndrome and identify opportunities to reduce progression or alleviate disabling symptoms.

In conclusion, among patients with acute proximal deep-vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding.

Supported by grants from the National Heart, Lung, and Blood Institute (NHLBI) for the clinical coordinating center (U01-HL088476 to Washington University in St. Louis) and data coordinating center (U01-HL088118 to McMaster University, Hamilton, ON); the Washington University Center for Translational Therapies in Thrombosis, which is supported by a grant from the NHLBI (U54-HL112303); the Washington University Institute of Clinical and Translational Sciences, which is supported by a grant from the National Center for the Advancement of Translational Sciences (UL1-TR00044810); Boston Scientific; Covidien (now Medtronic); Genentech; the Society of Interventional Radiology Foundation; the Canada Research Chairs Program (Tier 1 support to Dr. Kahn); the CanVECTOR Network (funded by Canadian Institutes of Health Research, to Dr. Kahn); the Heart and Stroke Foundation of Canada (Investigator Award to Dr. Kearon); and a Jack Hirsh Professorship in Thrombosis (to Dr. Kearon). BSN Medical donated the compression stockings.

Dr. Vedantham reports receiving grant support from Cook Medical and Volcano; Dr. Goldhaber, receiving grant support from Bio2 Medical and grant support and consulting fees from Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Portola, Bayer, and BTG/Ekos; Dr. Kahn, receiving advisory board fees from Bayer and BMS Pfizer; Dr. Jaff, holding equity in Embolitech and Venarum and serving as an uncompensated advisor for Boston Scientific, Cordis Corporation, and Medtronic; Dr. Cohen, receiving grant support from Abbott Vascular and Boston Scientific, consulting fees from Cardinal Health, and grant support and consulting fees from Medtronic; Dr. Razavi, receiving consulting fees from Boston Scientific; Dr. Comerota, receiving consulting fees from Medtronic; Dr. Blinder, receiving honoraria from Janssen Pharmaceuticals; Dr. Sacks, receiving consulting fees from Teleflex; Dr. Rundback, receiving fees for chairing a

committee for Biotronic, consulting fees and serving as a principal investigator for Symbionix, lecture fees from Gore and Abbott, lecture fees and grant support from Cook, lecture fees and consulting fees from Cardiovascular Systems, grant support paid to his institution from Juvantas, Daichii Sankyo, Mercator, Bard, Intact, and Atrium, fees for serving on the board of VIVA Physicians, lecture fees, serving on a scientific advisory board, grant support, and serving as a course director and principal investigator for Medtronic, and serving on a scientific advisory board for Boston Scientific; and Dr. Garcia, receiving grant sup-

port and lecture fees from Boston Scientific, grant support, lecture fees, and donated materials from Ekos/BTG, and lecture fees and donated materials from Cook. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Andrei Kindzelski (NHLBI Project Officer) and the entire network of investigators and study staff at the coordinating centers, core laboratories, and clinical centers (a list is provided in the Supplementary Appendix).

APPENDIX

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REFERENCES

- Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004;141:249-56.
- Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008;149:698-707.
- Enden T, Haig Y, Kløw NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomized controlled trial. *Lancet* 2012;379:31-8.
- Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet* 2014;383:880-8.
- Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost* 2008;6:1105-12.
- Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. *Ann Surg* 2004;239:118-26.
- Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev* 2016;11:CD002783.
- Plate G, Akesson H, Einarsson E, Ohlin P, Eklöf B. Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula. *Eur J Vasc Surg* 1990;4:483-9.
- Vedantham S, Grassi CJ, Ferral H, et al. Reporting standards for endovascular treatment of lower extremity deep vein thrombosis. *J Vasc Interv Radiol* 2006;17:417-34.
- Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. *Radiology* 1994;191:487-94.
- Vedantham S, Vesely TM, Sicard GA, et al. Pharmacomechanical thrombolysis and early stent placement for iliofemoral deep vein thrombosis. *J Vasc Interv Radiol* 2004;15:565-74.
- Cynamon J, Stein EG, Dym RJ, Jagust MB, Binkert CA, Baum RA. A new method for aggressive management of deep vein thrombosis: retrospective study of the power pulse technique. *J Vasc Interv Radiol* 2006;17:1043-9.
- Hilleman DE, Razavi MK. Clinical and economic evaluation of the Trellis-8 infusion catheter for deep vein thrombosis. *J Vasc Interv Radiol* 2008;19:377-83.
- Vedantham S, Goldhaber SZ, Kahn SR, et al. Rationale and design of the ATTRACT Study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis. *Am Heart J* 2013;165(4):523-530.e3.
- Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e419S-e496S.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315-52.
- Vedantham S, Thorpe PE, Cardella JF, et al. Quality improvement guidelines for the treatment of lower extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol* 2006;17:435-47.
- Vedantham S, Sista AK, Klein SJ, et al. Quality improvement guidelines for the treatment of lower-extremity deep vein thrombosis with use of endovascular thrombus removal. *J Vasc Interv Radiol* 2014;25:1317-25.
- Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. *J Thromb Haemost* 2009;7:884-8.
- Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost* 2009;7:879-83.
- Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the Venous Clinical Severity Score: venous outcomes consensus

- statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. *J Vasc Surg* 2010; 52:1387-96.
22. Ware JE, Kosinski M, Keller S. SF-36 physical and mental summary measures: a user's manual. Boston: The Health Institute, New England Medical Center, 1994.
 23. Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. *J Vasc Surg* 2003;37: 410-9.
 24. Bernstein SL, Bijur PE, Gallagher EJ. Relationship between intensity and relief in patients with acute severe pain. *Am J Emerg Med* 2006;24:162-6.
 25. Marder VJ, Soulen RL, Atichartakarn V, et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. *J Lab Clin Med* 1977;89:1018-29.
 26. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
 27. Brandjes DPM, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997;349:759-62.
 28. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med* 1996;125:1-7.
 29. van Dongen CJJ, Prandoni P, Frulla M, Marchiori A, Prins MH, Hutten BA. Relation between quality of anticoagulant treatment and the development of the post-thrombotic syndrome. *J Thromb Haemost* 2005;3:939-42.
 30. AbuRahma AF, Perkins SE, Wulu JT, Ng HK. Iliofemoral deep vein thrombosis: conventional therapy versus lysis and percutaneous transluminal angioplasty and stenting. *Ann Surg* 2001;233:752-60.
 31. Elliot MS, Immelman EJ, Jeffery P, et al. A comparative randomized trial of heparin versus streptokinase in the treatment of acute proximal venous thrombosis: an interim report of a prospective trial. *Br J Surg* 1979;66:838-43.
 32. Arnesen H, Høiseth A, Ly B. Streptokinase of heparin in the treatment of deep vein thrombosis: follow-up results of a prospective study. *Acta Med Scand* 1982; 211:65-8.
 33. Turpie AGG, Levine MN, Hirsh J, et al. Tissue plasminogen activator (rt-PA) vs heparin in deep vein thrombosis: results of a randomized trial. *Chest* 1990;97: Suppl:172S-175S.
 34. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. *Lancet Haematol* 2016;3(2):e64-e71.
 35. Mewissen MW, Seabrook GR, Meissner MH, Cynamon J, Labropoulos N, Haughton SH. Catheter-directed thrombolysis for lower extremity deep venous thrombosis: report of a national multicenter registry. *Radiology* 1999;211:39-49.
 36. Bashir R, Zack CJ, Zhao H, Comerota AJ, Bove AA. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone to treat lower-extremity proximal deep vein thrombosis. *JAMA Intern Med* 2014;174: 1494-501.
 37. Robertson L, Kesteven P, McCaslin JE. Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep vein thrombosis. *Cochrane Database Syst Rev* 2015;30:CD010956.

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