

**After the ATTRACT study,
has the management of acute deep vein
thrombosis of the iliofemoral veins
changed?**

**IS STILL POSSIBLE TO RECOMMEND
PHARMACOMECHANICAL THROMBOLYSIS?**



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Journal of Vascular Surgery

**After the ATTRACT study,
the management of acute deep vein thrombosis
of the iliofemoral veins
DID NOT CHANGE!**

**YES! IT IS STILL POSSIBLE TO RECOMMEND
PHARMACOMECHANICAL THROMBOLYSIS!**



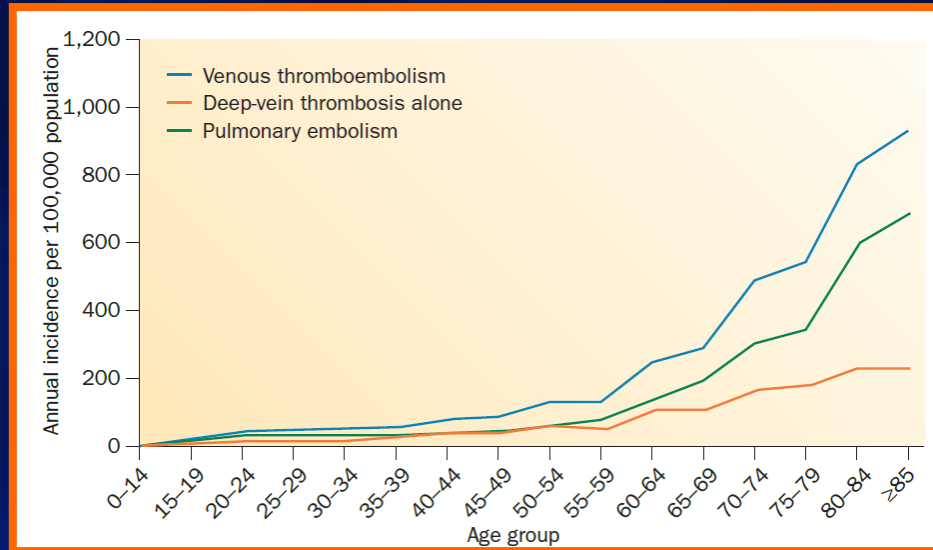
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No Conflict of Interest

ACUTE VENOUS THROMBOEMBOLISM

DVT & PE



Heit, J. A. *Nat. Rev. Cardiol.* **12**, 464–474 (2015)

- Occurs as often as stroke (1 per 1000/year)
- Death due to PE: > 100,000/year
- ~ 30% of VTE patients have recurrence
- 28% to 49% will develop post-thrombotic syndrome

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

S. Vedantham, S.Z. Goldhaber, J.A. Julian, S.R. Kahn, M.R. Jaff, D.J. Cohen, E. Magnuson, M.K. Razavi, A.J. Comerota, H.L. Gornik, T.P. Murphy, L. Lewis, J.R. Duncan, P. Nieters, M.C. Derfler, M. Filion, C.-S. Gu, S. Kee, J. Schneider, N. Saad, M. Blinder, S. Moll, D. Sacks, J. Lin, J. Rundback, M. Garcia, R. Razdan, E. VanderWoude, V. Marques, and C. Kearon, for the ATTRACT Trial Investigators*

ABSTRACT

BACKGROUND

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

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.

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.)

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.

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

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The NEW ENGLAND
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Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT)

N ENGL J MED 377:23 NEJM.ORG DECEMBER 7, 2017

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

S. Vedantham, S.Z. Goldhaber, J.A. Julian, S.R. Kahn, M.R. Jaff, D.J. Cohen, E. Magnuson, M.K. Razavi, A.J. Comerota, H.L. Gornik, T.P. Murphy, L. Lewis, J.R. Duncan, P. Nieters, M.C. Derfler, M. Filion, C.-S. Gu, S. Kee, J. Schneider, N. Saad, M. Blinder, S. Moll, D. Sacks, J. Lin, J. Rundback, M. Garcia, R. Razdan, E. VanderWoude, V. Marques, and C. Kearon, for the ATTRACT Trial Investigators*

ABSTRACT

BACKGROUND

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

We randomly assigned 692 patients with acute proximal deep-vein thrombosis to receive either anticoagulation (control group) or anticoagulation plus pharmacomechanical thrombolysis (catheter-directed thrombolysis plus intrathrombus delivery of recombinant tissue plasminogen activator with or without stenting). The primary outcome was major bleeding, with or without stenting. The primary outcome was major bleeding, with or without stenting. The primary outcome was major bleeding, with or without stenting.

RESULTS

Between 6 and 24 months, there was no significant difference in the percentage of patients with the post-thrombotic syndrome between the pharmacomechanical-thrombolysis group and 48% in the control group (95% confidence interval [CI], 0.82 to 1.11; $P=0.10$). There were no more major bleeding events within 10 days of random assignment, but no significant difference in recurrent venous thrombosis at 24-month follow-up period (12% in the pharmacomechanical group vs 8% in the control group, $P=0.09$). Moderate to severe post-thrombotic syndrome occurred in 18% of patients in the pharmacomechanical group compared with 28% of those in the control group (risk ratio, 0.64; 95% CI, 0.48 to 0.86). Scores for the post-thrombotic syndrome were lower in the pharmacomechanical-thrombolysis group than in the control group ($P<0.01$ for the comparison of the Villalta score). There was no difference in quality of life from baseline to 24 months between the treatment groups.

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, pharmacomechanical catheter-directed thrombolysis was associated with a lower risk of the post-thrombotic syndrome and moderate to severe post-thrombotic syndrome, but not with a lower risk of major bleeding. (Funded by the National Institutes of Health. NCT01472267. ATTRACT ClinicalTrials.gov number, NCT01472267.)

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

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ATTRACT TRIAL

- 692 patients with acute proximal DVT (iliofemoral or femoro-popliteal)
- Randomized to anticoagulation (AC) vs. AC + pharmacomechanical catheter-directed thrombolysis (PCDT)

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

S. Vedantham, S.Z. Goldhaber, J.A. Julian, S.R. Kahn, M.R. Jaff, D.J. Cohen, E. Magnuson, M.K. Razavi, A.J. Comerota, H.L. Gornik, T.P. Murphy, L. Lewis, J.R. Duncan, P. Nieters, M.C. Derfler, M. Filion, C.-S. Gu, S. Kee, J. Schneider, N. Saad, M. Blinder, S. Moll, D. Sacks, J. Lin, J. Rundback, M. Garcia, R. Razdan, E. VanderWoude, V. Marques, and C. Kearon, for the ATTRACT Trial Investigators*

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The post-thrombotic syndrome frequently develops in patients with proximal deep-vein thrombosis despite treatment with anticoagulation 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 654 patients with proximal deep-vein thrombosis to receive either anticoagulation alone (control group) or pharmacomechanical thrombolysis (catheter-mediated thrombolysis plus systemic anticoagulation) plus intracatheter delivery of recombinant tissue plasminogen activator (pharmacomechanical thrombolysis), with or without stenting. The primary outcome was post-thrombotic syndrome between 6 and 24 months of follow-up.

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RESULTS

Between 6 and 24 months, there was no significant difference in the percentage of patients with the post-thrombotic syndrome between the pharmacomechanical-thrombolysis group and 48% in the control group (hazard ratio, 0.82; 95% confidence interval [CI], 0.82 to 1.11; $P=0.5$). There was no significant difference in the number of major bleeding events within 10 days of random assignment, but no significant difference in recurrent venous thrombosis during the 24-month follow-up period (12% in the pharmacomechanical group vs 8% in the control group, $P=0.09$). Moderate to severe ulceration occurred in 18% of patients in the pharmacomechanical group vs 11% of those in the control group (risk ratio, 1.6; 95% CI, 1.1 to 2.3; $P=0.01$). Scores for the post-thrombotic syndrome were significantly lower in the pharmacomechanical-thrombolysis group than in the control group ($P<0.01$ for the comparison of the Villalta score). There was no significant difference in quality of life from baseline to 24 months between the treatment groups.

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, pharmacomechanical catheter-directed thrombolysis was associated with a lower risk of the post-thrombotic syndrome and moderate to severe major bleeding. (Funded by the National Institutes of Health; ATTRACT ClinicalTrials.gov number, NCT01706382.)

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ATTRACT Trial

Primary Outcome

Development of the post-thrombotic syndrome between 6 and 24 months:

- Villalta score ≥ 5
- Ulcer
- Unplanned endovascular procedure beyond 6 months

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

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

METHODS

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.

RESULTS

Between 6 and 24 months, there was no significant difference in the percentage of patients with the post-thrombotic syndrome between pharmacomechanical thrombolysis (47%) and 48% in the control group (95% confidence interval [CI], -1.1; $P=0.56$). There was no difference in the risk of major bleeding (1.7% vs. 0.3% at 24 months of follow-up; $P=0.049$) but no significant difference in the risk of major bleeding at 6 months (10% vs. 8% in the control group; $P=0.10$). There was no difference in the occurrence of major bleeding in 18% of patients in the pharmacomechanical thrombolysis group and 18% of those in the control group. There was no difference in the scores for the post-thrombotic syndrome between the pharmacomechanical thrombolysis group and the control group ($P<0.01$ for the comparison of the mean in quality of life from baseline to 24 months in the treatment groups).

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, pharmacomechanical catheter-directed thrombolysis was associated with a lower risk of the post-thrombotic syndrome and a lower risk of major bleeding. (Funded by the National Institutes of Health; ATTRACT ClinicalTrials.gov number, NCT01533307.)

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ATTRACT
Trial

- Post-thrombotic syndrome :NO difference (47% vs. 48%% P=0.56).
- Major bleeding: More with PCDT (1.7% vs. 0.3%, P=0.049),
- NO improvement in at 24 months

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ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

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ABSTRACT

BACKGROUND

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

METHODS

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.

RESULTS

Between 6 and 24 months, there was no significant difference in the percentage of patients with the post-thrombotic syndrome between the pharmacomechanical-thrombolysis group and 48% in the control group (95% confidence interval [CI], 0.11; $P=0.50$). There was no significant difference in the risk of more major bleeding (within 10 days of random assignment) between the two groups, but no significant difference in the risk of major bleeding at 24-month follow-up (8% in the control group vs 18% in the pharmacomechanical-thrombolysis group). Scores for the post-thrombotic syndrome were lower in the pharmacomechanical-thrombolysis group than in the control group ($P<0.01$ for the comparison of the mean in quality of life from baseline between the treatment groups).

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, pharmacomechanical catheter-directed thrombolysis was associated with a lower risk of the post-thrombotic syndrome and major bleeding. (Funded by the National Institutes of Health; ATTRACT ClinicalTrials.gov number, NCT01402443.)

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ATTRACT
RCT

- Recurrent VTE: NO difference (12% vs. 8%, $P=0.09$).
- Moderate-to-severe post-thrombotic syndrome: 18% of PCDT patients vs 24% of Controls (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 PCDT group ($P<0.01$).

ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

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

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.

RESULTS

Between 6 and 24 months, there was no significant difference in the percentage of patients with the post-thrombotic syndrome in the pharmacomechanical-thrombolysis group and 48% in the control group (95% confidence interval [CI], 0.82 to 1.11; $P=0.12$). There was no significant difference in the risk of more major bleeding events within 30 days of random assignment (12% vs 8% in the control group, $P=0.09$). Major bleeding occurred in 18% of patients in the pharmacomechanical-thrombolysis group and 12% of those in the control group. Mean scores for the post-thrombotic syndrome were significantly higher in the pharmacomechanical thrombolysis group than in the control group ($P<0.01$ for the comparison). There was no difference in quality of life between the treatment groups.

CONCLUSION

Among patients with acute proximal deep-vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not lower the risk of the post-thrombotic syndrome or major bleeding. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01100061.)

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ATTRACT RCT

Conclusion

Among patients with acute proximal DVT, the addition of PCDT to AC did not lower the risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding.

ORIGINAL ARTICLE

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

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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

We randomly assigned 692 patients with acute proximal deep-vein thrombosis to receive either anticoagulation alone (control group) or anticoagulation plus pharmacomechanical thrombolysis. The primary end point was the risk of major bleeding, with or without thrombolysis. The primary secondary end point was the risk of post-thrombotic syndrome at 24 months.

RESULTS

Between 6 and 24 months, the percentage of patients with the post-thrombotic syndrome was significantly lower in the pharmacomechanical-thrombolysis group than in the control group (confidence interval [CI], 0.82 to 1.00), with no more major bleeding events with thrombolysis than without, but no significant difference in recurrence of proximal deep-vein thrombosis at the 24-month follow-up period (12% in the pharmacomechanical-thrombolysis group vs 8% in the control group, $P=0.09$). Moderate to severe venous claudication occurred in 18% of patients in the pharmacomechanical-thrombolysis group and in 18% of those in the control group (risk ratio, 0.73). Mean Villalta scores for the post-thrombotic syndrome were significantly lower in the pharmacomechanical-thrombolysis group than in the control group at 24 months ($P<0.01$ for the comparison of the Villalta scores at 24 months). There was no significant difference in quality of life from baseline to 24 months between the treatment groups.

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, pharmacomechanical catheter-directed thrombolysis was associated with a lower risk of the post-thrombotic syndrome and moderate to severe venous claudication, but not with a lower risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00790000.)

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ATTRACT Trial

Problems

1. Villalta Scale (subjective scale, not good to measure changes in venous claudication)
2. Primary endpoint (did not focus on symptom improvement, used a binary method:yes/no)
3. Enrolled femoropopliteal DVT patients (43%)
4. Slow recruitment, few patients per center (1.2 treated patient/center /year).

ORIGINAL ARTICLE

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BACKGROUND

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

METHODS

We randomly assigned 500 patients with proximal deep-vein thrombosis to receive either anticoagulation alone or anticoagulation plus pharmacomechanical thrombolysis (catheter-mediated or ultrasound-assisted thrombolysis with or without stenting). The primary end point was the occurrence of post-thrombotic syndrome between 6 and 24 months.

RESULTS

Between 6 and 24 months, there was no significant difference in the percentage of patients with the post-thrombotic syndrome between the pharmacomechanical-thrombolysis group and the anticoagulation group (odds ratio and confidence interval [CI], 0.82 to 1.47; $P=0.42$). There was no difference in the number of major bleeding events with or without major bleeding but no significant difference in rebleeding between the groups during the 24-month follow-up period (12% vs 10%; $P=0.09$). Major bleeding occurred in 18% of patients in the pharmacomechanical-thrombolysis group and in 15% of those in the control group (risk scores for the post-thrombotic syndrome were lower in the pharmacomechanical-thrombolysis group than in the control group; $P<0.01$ for the comparison of the groups). There was no difference in the improvement in quality of life from baseline between the treatment groups.

CONCLUSIONS

Among patients with acute proximal deep-vein thrombosis, pharmacomechanical catheter-directed thrombolysis did not reduce the risk of the post-thrombotic syndrome or major bleeding. (Funded by the National Institutes of Health; ATTRACT ClinicalTrials.gov number, NCT01100062.)

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.

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

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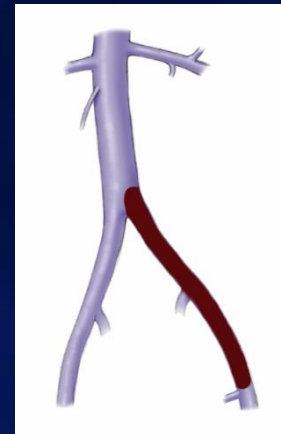
N ENGL J MED 377:23 NEJM

ATTRACT
RCT

5. 1 of every 50 patients screened entered the trial
6. Few (28%) venous stenting (62% balloon angioplasty!)
7. No unified protocol (Dose? Duration?)
8. IVUS/Multiplanar venography was not in the clinical protocol
9. 59% of PCDT only had CTD

ORIGINAL RESEARCH ARTICLE

Endovascular Thrombus Removal for Acute Iliofemoral Deep Vein Thrombosis Analysis From a Stratified Multicenter Randomized Trial

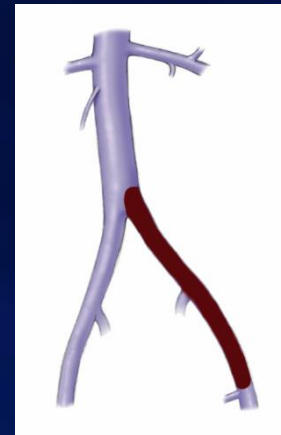


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Razavi, MD Andrei L. Kindzelski, MD, PhD, Riyaz Bashir, MD, Parag Patel, MD, Mel Sharafuddin, MD
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February 26, 2019
Circulation.
2019;139:1162–1173

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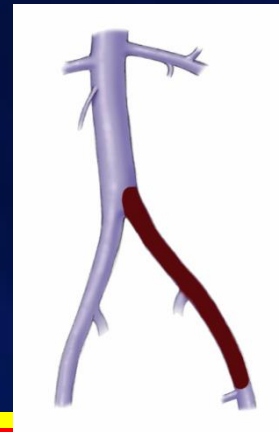
391 iliofemoral DVT patients randomized to PCDT with AC vs AC

- NO difference in PTS between 6 and 24 months
- PCDT significantly reduced
 - PTS severity
 - Number of patients with moderate-or-severe PTS
 - Number of patients with severe PTS

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February 26, 2019
Circulation.
2019;139:1162–1173

PCDT

- Decreased leg pain and swelling at 30 days
- Improved venous disease–specific quality of life through 24 months,
- NO difference in generic quality of life
- NO difference in major bleeding within 10 days (1.5% versus 0.5% ($P=0.32$))
- NO difference in recurrent VTE over 24 months

Editors' Choice



Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis

Check for updates

Susan R. Kahn, MD, MSc,^a Jim A. Julian, MMath,^{b,c} Clive Kearon, MB, PhD,^{c,d} Chu-Shu Gu, PhD,^{b,c} David J. Cohen, MD, MSc,^{e,f} Elizabeth A. Magnuson, ScD,^f Anthony J. Comerota, MD,^g Samuel Z. Goldhaber, MD,^{h,j} Michael R. Jaff, DO,^{ij} Mahmood K. Razavi, MD,^k Andrei L. Kindzelski, MD, PhD,^l Joseph R. Schneider, MD, PhD,^m Paul Kim, MD,ⁿ Rabih Chaer, MD,^o Akhilesh K. Sista, MD,^p Robert B. McLafferty, MD,^q John A. Kaufman, MD,^r Brandt C. Wible, MD,^s Morey Blinder, MD,^t and Suresh Vedantham, MD,^u for the ATTRACT Trial Investigators, Montreal, Quebec, and Hamilton, Ontario, Canada; Kansas City and St. Louis, Mo; Alexandria, Va; Boston and Newton, Mass; Orange, Calif; Bethesda, Md; Chicago, Ill; Portland, Me; Pittsburgh, Pa; New York, NY; and Portland, Ore

Journal of
Vascular Surgery
Venous and Lymphatic Disorders

✓ In patients with proximal DVT, PCDT resulted in greater improvement in disease-specific QOL than no PCDT, at 1 month and 6 months, but not later.

J Vasc Surg Venous Lymphat Disord,

January 2020



Quality of life after pharmacomechanical catheter-directed thrombolysis for proximal deep venous thrombosis

Check for updates

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- ✓ In patients with proximal DVT, PCDT resulted in greater improvement in disease-specific QOL than no PCDT, at 1 month and 6 months, but not later.
- ✓ In patients with iliofemoral DVT, PCDT led to greater improvement in disease-specific QOL during 24 months.

J Vasc Surg Venous Lymphat Disord,

January 2020

The ATTRACTiveness of catheter-directed thrombolysis



Efthymios D. Avgerinos, MD, and Rabih A. Chaer, MD, MSc, Pittsburgh, Pa

The long-anticipated results of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial have challenged the expectations of catheter-directed thrombolysis (CDT) believers, demonstrating a relatively high post-thrombotic rate irrespective of treatment modality (47% for CDT vs 48% for anticoagulation at 2 years; $P = .56$).¹ In addition to the invasive nature of CDT, higher (although still low [1.7%]) major bleeding complications were seen. However, CDT reduced early deep venous thrombosis (DVT) symptoms and the severity of post-thrombotic syndrome (PTS). Whereas the study is unique and sets the benchmark for the treatment of acute iliofemoral DVT, there should be caution in the interpretation as selection bias and dilution of the sample with softly indicated cases may have skewed the results.

Who were the patients enrolled? It is rather likely that interventionalists avoided enrolling or randomizing patients that they "felt" would benefit from CDT (eg, patients with persistent symptoms despite being on anticoagulation). The study did not include consecutive eligible patients, and the ratio of presenting to screened DVTs was most likely too high. Interestingly, 1100 patients declined participation in the study, many of whom could have presented with severe symptoms and refused randomization.

Why were femoropopliteal DVTs included? The inclusion of patients with only a femoropopliteal DVT who still have good outflow through the common femoral vein may have influenced the outcome negatively, as conservative treatment in these patients is not expected to perform poorly. Partial or complete recanalization of the femoral segment is seen in almost 80% of patients after 6 months.² The iliofemoral segment, on the other hand, will recanalize only in 20% of cases at 5 years.³ In a prospective study of patients with acute

DVT treated with anticoagulation alone, the most powerful predictor of PTS was iliofemoral DVT, whereas femoral DVT was not.⁴ Inclusion of the femoropopliteal DVTs in the ATTRACT trial may have given us the answer that femoropopliteal DVTs should not be lysed, which is what current clinical practice is, but they have diluted and skewed the study in favor of anticoagulation. The subgroup analysis for iliofemoral DVT did not show a difference, but ATTRACT was not powered for this analysis.

The significant reduction of PTS severity with CDT should not be underestimated (risk ratio, 0.73; 95% confidence interval, 0.54-0.98; $P = .04$). PTS was defined as Villalta score >4 . As such, patients with mild symptoms (itching, mild edema) were as frequent in the CDT group as in the anticoagulation group. In assessing an invasive vs a noninvasive DVT treatment, moderate to severe PTS might have been a more appropriate primary end point. Secondary analysis of other data, such as the relation of PTS to the percentage of clot resolution after CDT (open vein hypothesis) and to the patency rates of the thrombosed segments, may be more informative, as well as the 5-year data.

Another randomized trial enrolling consecutive patients with iliofemoral DVT is under way, Catheter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT (DUTCH CAVA-trial), despite being powered for any PTS and targeting a smaller sample, it may offer further insight into the role of CDT. Until then, catheter-directed interventions should still remain in the treatment armamentarium for patients with symptomatic iliofemoral DVT with good life expectancy and low bleeding risk.

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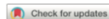
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The ATTRACTiveness of catheter-directed thrombolysis

Eftymios D. Avgerinos, MD, and Rabih A. Chaer, MD, MSc, Pittsburgh, Pa



The long-anticipated results of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial have challenged the expectations of catheter-directed thrombolysis (CDT) believers, demonstrating a relatively high post-thrombotic rate irrespective of treatment modality (47% for CDT vs 48% for anticoagulation at 2 years, $P = .56$).¹ In addition to the invasive nature of CDT, higher (although still low [1.7%]) major bleeding complications were seen. However, CDT reduced early deep venous thrombosis (DVT) symptoms and the severity of post-thrombotic syndrome (PTS). Whereas the study is unique and sets the benchmark for the treatment of acute iliofemoral DVT, there should be caution in the interpretation as selection bias and dilution of the sample with softly indicated cases may have skewed the results.

Who were the patients enrolled? It is rather likely that interventionalists avoided enrolling or randomizing patients that they "felt" would benefit from CDT (eg, patients with persistent symptoms despite being on anticoagulation). The study did not include consecutive eligible patients, and the ratio of presenting to screened DVTs was most likely too high. Interestingly, 1100 patients declined participation in the study, many of whom could have presented with severe symptoms and refused randomization.

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The significant reduction of PTS should not be underestimated (risk difference interval, 0.54-0.98; $P = .04$). Villalta score >4 . As such, patients with mild symptoms (itching, mild edema) were as frequent as in the anticoagulation group. In a study comparing a noninvasive DVT treatment, rDVT might have been a more appropriate endpoint. Secondary analysis of other definitions of PTS to the percentage of clot (open vein hypothesis) and to the percentage of thrombosed segments, may be more relevant.

Another randomized trial enrolling patients with iliofemoral DVT is underway. Anticoagulation Alone for Acute Proximal DVT (DUTCH CAVA-trial); despite being a smaller study and targeting a smaller sample, it provides insight into the role of CDT. Undirected interventions should still be reserved for patients with iliofemoral DVT with good life expectancy and low bleeding risk.

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EDITORIAL

The Attract Trial: A Step Forward for Evidence Based DVT Care

The ATTRACT Trial was a 56 centre, randomised controlled trial (RCT) that evaluated pharmacomechanical catheter directed thrombolysis (PCDT) for prevention of post-thrombotic syndrome (PTS) in patients with acute proximal deep vein thrombosis (DVT).¹ The study found that PCDT (1) did not prevent PTS over 2 years (primary outcome); (2) increased major bleeding; (3) did not influence health related quality of life (QOL) or recurrent venous thromboembolism; (4) improved leg pain and swelling over 30 days; and (5) reduced the severity of PTS.

To understand these results, it is crucial to recall what question the study was designed to answer. In clinical practice, DVT patients are initially anticoagulated. Most patients improve, but some develop progressive symptoms, thrombus extension, and/or severe activity limitation, and may be referred for PCDT. Patients in this highly selected sub-population are more likely to (1) be poor responders to initial anticoagulation; (2) have severe symptoms and extensive iliofemoral DVT, with or without an iliac vein stenosis; and (3) receive PCDT many days after symptom onset, when acute and subacute clots are present.

In contrast, in ATTRACT, PCDT was offered as *first line treatment* for DVT along with anticoagulation. The severity of symptoms, initial response to anticoagulation, and thrombus burden were not used as study entry criteria. Hence, ATTRACT included many patients who are not typically referred for PCDT in clinical practice. Indeed, this was the whole point of the study: we were not seeking to validate the existing use of PCDT as "salvage" therapy; rather, ATTRACT was boldly intended to determine if PCDT should be extended as *routine first line therapy* to a much larger and broader cohort of DVT patients.

With this core understanding, the study's conduct and findings became clearer. Some physicians believe that iliac vein stenting was underused. In fact, the protocol encouraged stenting of iliac vein lesions causing $\geq 50\%$ venous diameter narrowing, mean pressure gradient >2 mmHg, or robust collateral filling; operators were required to show experience and comfort with iliac vein stenting; and many were actually early advocates of a highly proactive posture towards stenting.² Rather, the use of stents in ATTRACT probably relates to the above noted differences between the study population and our clinical practice. One would expect fewer patients to have iliac vein stenosis because (1) 43% had or

DVT; (2) we did not restrict enrollment only to poor responders to anticoagulation (which may predict a lesion); and (3) we lysed patients at a median of 6 days after symptom onset, when very few patients would have lysis resistant subacute thrombus.

In fact, the endovascular operators performed well. Safety (just 1.4% additional major bleeds) was better than previous CDT/PCDT studies, and clot removal (mean post-lysis modified Marder score 2.7 out of 24 maximum points) was similar to previous studies.^{3,4} We did not capture data on the intensity of anticoagulation delivered during PCDT, but the largely successful thrombus removal and low rate of early re-thrombosis suggest that it was adequate. We did not observe between-arm differences in use of anticoagulant therapy during follow up.

PTS exhibits diverse clinical phenotypes and has no diagnostic gold standard, so we used a Villalta PTS score ≥ 5 as our primary outcome measure, per international guidelines.⁵ However, a major strength of the study was its use of *multiple* venous outcome measures. Even using the Venous Clinical Severity Scale, there was no significant difference in PTS rates (30% PCDT vs. 36% control). QOL assessment using two validated measures found no benefit from use of PCDT in the overall study population, consistent with a previous RCT.⁶

Some ATTRACT findings hint at likely differences in PCDT effect between patients with iliofemoral DVT versus femoral-popliteal DVT; we continue to explore the magnitude, statistical significance, and clinical importance of such subgroup effects. The inclusion of patients with femoral-popliteal DVT was well justified because they are at high risk of PTS, because previous studies suggested that they may benefit from clot removal, and because some practitioners were exposing these patients to the risks of thrombolysis.

ATTRACT featured unprecedented precautions against bias: central randomisation, stratification by thrombus extent, blinding of assessors and adjudicators, control of confounders, independent data management, and rigorous site monitoring and data verification against source documents. The study's size, diverse physician subspecialty involvement, and rigorous design should encourage strong

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

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Just How Attractive is the ATTRACT Trial?

Gerard J. O'Sullivan¹ · Rick de Graaf² · Steven A. Black³

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Abstract Venous thromboembolism (VTE) is a major public health issue; deep vein thrombosis (DVT) affects about 1/1000 patients. Each year, VTE kills more patients in Western Europe than breast cancer, prostate cancer, acquired immune deficiency syndrome (AIDS) and road traffic accidents combined and is responsible for the deaths of approximately 370,000 European citizens (Cohen et al. in *Thromb Haemostasis* 98:756–764, 2007; Bělohávek et al. in *Exp Clin Cardiol* 18(2):129–138, 2013). The recently published ATTRACT trial (Acute Venous Thrombosis Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) (Vedantham et al. in *N Engl J Med* 377:2240–2252, 2017) concluded that the addition of catheter-directed thrombolysis to standard therapy with anticoagulation and compression stockings offers no significant clinical benefit over standard therapy in terms of reduction in the rate of post-thrombotic syndrome (PTS) at 2 years. It is the largest, prospective, multi-centre, randomised controlled trial (RCT) and represents the culmination over a decade of planning, execution and analysis. In this opinion article, we analyse why it was needed, what it demonstrated, some limitations, and the directions in which this important publication will take us.

Keywords Deep venous thrombosis · Catheter directed thrombolysis · Pharmaco-Mechanical venous thrombectomy · Review

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Introduction

Why was ATTRACT Needed?

The current gold standard of anticoagulation (AC) dates largely from a single randomised trial in 1960, demonstrating that anticoagulation improved the mortality and reduced the incidence of pulmonary embolus [4, 5] in patients suffering from acute deep vein thrombosis (DVT).

Over time, it was realised that despite adequate anticoagulation, patient morbidity was considerable, with a high rate of post-thrombotic syndrome (PTS), and a landmark paper by O'Donnell et al. [6] in 1977 eloquently demonstrated the practical, socio-economic implications of an ilio-femoral DVT—at 10 years nearly 50% of patients had ulcers, 11 of 12 men were disabled and unable to maintain a steady job because of their leg symptoms and 7 of 9 women were unable to perform household duties.

Around this time, systemic thrombolysis was considered for the treatment of deep vein thrombosis, and multiple trials had already demonstrated improved rates of venous patency, however, at the cost of increased rates of bleeding which significantly impacted on the viability of this approach [7].

During the same period, large cardiology trials demonstrated improved rates of survival in acute myocardial infarction for systemic thrombolysis as opposed to standard therapy. The benefits in these trials did outweigh the risks [8].

Vascular specialists felt that similar benefits might apply to deep veins if the thrombolytic agent was confined to the thrombosed area, and so catheter-directed thrombolysis became the focus of intense efforts. Results from a small experience in Stanford from 1994 [9] paved the way for the

Just How Attractive is the ATTRACT Trial?

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Check for updates

Editorial

The ATTRACT trial may seem more attractive than it first looks for the management of acute deep vein thrombosis!

Thomas M Aherne¹ , Stewart R Walsh¹, Gerry J O'Sullivan², Alun H Davies³ and Tjun Y Tang⁴

Post-thrombotic syndrome (PTS) affects almost half of patients who develop deep venous thrombosis (DVT) and represents a significant impediment to both patient functionality¹ and healthcare costing.² The syndrome manifests as a result of dysfunctional venous outflow, with the ensuing tissue oedema resulting in an acute inflammatory response within the interstitium. This in turn causes the spectrum of debilitating symptoms known as PTS, which may eventually lead to tissue loss.³

With persistent outflow obstruction, a predictor of future PTS,⁴ the aim of the pharmacomechanical venous intervention is to reduce thrombus burden and hence maintain an 'open vein' with the hypothesis that this reduces chronic obstructive symptomatology. However, there remains a paucity of level-one data addressing its use.

The recent publication of the Acute Venous Thrombolysis: Thrombus Removal with Catheter-Directed Thrombolysis (ATTRACT) trial⁵ has provided venous interventionists with more robust evidence to guide the management of patients with acute ilio-femoral DVT. This powered multi-centre trial represents the largest dataset to address this challenging patient cohort with participants randomised to pharmacomechanical thrombolysis plus standard treatment or standard treatment alone. Interventions involved initial catheter-directed thrombolysis (CDT) and either interval or immediate thrombectomy with stenting reserved for those with a residual 50% venous stenosis following thrombus extraction. The primary outcome was the development of PTS at 6–24 months as defined by the validated Villalta score,⁶ limb ulceration or need for further deep venous intervention. Further outcomes included severity of PTS, quality of life (QOL) and importantly major bleeding events. The findings of this long-term and ambitious randomised controlled trial (RCT) undoubtedly raise more questions than it answers, and there is a need for

additional prospective data to determine the best management strategies for specific patient cohorts. In contrast with the existing data,^{7–9} Vedantham et al.⁵ identified no difference between groups with regard to the reported PTS (47% vs. 48%, $p=0.56$) at 24 months. This may have been down to the design of the trial, which included patients with acute DVT not only within the femoro-popliteal segments but also those with more proximal iliac thrombosis. If enrolment had been limited to ilio-femoral cases, in which there is a higher risk of developing late PTS, the study may have had a higher probability of meeting the primary outcome measure. Thus, while the ATTRACT study recruited significantly more proximal DVT patients than previous RCTs,^{7,8,10} it may well be underpowered to offer definitive PTS outcome data. Of note, subgroup analysis did suggest that the severity of PTS was significantly lower in the study cohort at all timepoints compared to the control. However, intervention offered no improvement in QOL compared to standard therapy with the added detriment of higher peri-procedural major bleed rates (1.7% vs. 0.3%, $p=0.049$).

Indeed, the ATTRACT primary outcome contrasts, to some degree, previous well-regarded evidence examining the use of endovenous intervention.

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EDITORIAL

Results of the ATTRACT trial do not change the management of acute deep vein thrombosis

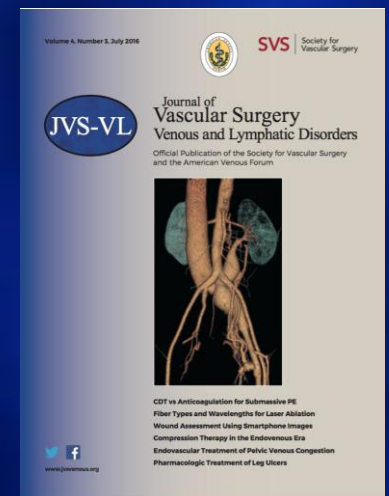
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The recent presentation of the primary results from the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial has sparked renewed interest in the appropriate indications for interventional therapy for acute lower extremity deep venous thrombosis (DVT).¹ Predictably, the findings of this ambitious long-term prospective randomized trial have raised more questions than they have

patients in this subset treated with anticoagulation alone. Also, those presenting with severe symptoms experienced more rapid resolution of symptoms in the first 30 days after PCDT compared with the control. The ATTRACT trialists cautioned that the study was not powered to draw definitive conclusions from these secondary analyses, so these findings should be confirmed by future research.

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Early thrombus removal strategies for acute deep venous thrombosis: Clinical Practice Guidelines of the Society for Vascular Surgery and the American Venous Forum

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Background: The anticoagulant treatment of acute deep vein thrombosis (DVT) is essential for the prevention of recurrent thrombotic events and the prevention of the post-thrombotic syndrome. The purpose of this guideline is to provide recommendations for the use of early thrombus removal strategies in patients with acute DVT.

Objective: A committee of experts from the Society for Vascular Surgery and the American Venous Forum to develop evidence-based recommendations for the use of early thrombus removal strategies in patients with acute DVT.

Methods: Evidence-based recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Recommendations were graded as strong (1) or weak (2) based on the quality of the evidence.

Results: On the basis of the best evidence, we recommend the use of early thrombus removal strategies in patients with acute DVT in favor of more proximal venous segments (Grade 1A). We further recommend their use in patients with limb-threatening ischemia due to iliofemoral venous outflow obstruction (Grade 1A). We suggest pharmacomechanical thrombolysis in patients with acute DVT if available and that surgical thrombectomy in patients with acute DVT if available.

Conclusions: Most data regarding early thrombus removal strategies are of low to moderate quality. Additional evidence becomes available.

- We suggest the use of early thrombus removal strategies in ambulatory patients with good functional capacity and a first episode of iliofemoral DVT of <14 days in duration (Grade 2C)
- We strongly recommend their use in patients with limb-threatening ischemia due to iliofemoral venous outflow obstruction (Grade 1A).

Take Home Message

PCDT is a reasonable treatment in selected symptomatic patients with iliofemoral DVT, who have low bleeding risk, and a willingness to undergo a catheter-based procedure after discussion of the benefits and risks.

**After the ATTRACT study,
the management of acute deep vein thrombosis
of the iliofemoral veins
DID NOT CHANGE!**

**IT IS STILL POSSIBLE TO RECOMMEND
PHARMACOMECHANICAL THROMBOLYSIS!**

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**THANK
YOU!**

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