ARTICLE IN PRESS

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

In-Hospital Risks and Management of Deep Venous Thrombosis According to Location of the Thrombus

Paul D Stein, MD, Fadi Matta, MD, Mary J. Hughes, DO

Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, East Lansing.

ABSTRACT

BACKGROUND: Whether deep venous thrombosis involving the pelvic veins or inferior vena cava is associated with higher in-hospital mortality or higher prevalence of in-hospital pulmonary embolism than proximal or distal lower extremity deep venous thrombosis is not known.

METHODS: This was a retrospective cohort study based on administrative data from the Nationwide Inpatient Sample, 2016, 2017. Patients hospitalized with a primary diagnosis of deep venous thrombosis at known locations were identified by International Classification of Diseases-10-Clinical Modification codes.

RESULTS: In-hospital all-cause mortality with deep venous thrombosis involving the inferior vena cava in patients treated only with anticoagulants was 2.2% versus 0.8% with pelvic vein deep venous thrombosis ($p<0.0001$), 0.7% with proximal deep venous thrombosis ($p<0.0001$) and 0.2% with distal deep venous thrombosis ($p<0.0001$). Mortality with anticoagulants was similar with pelvic vein deep venous thrombosis compared with proximal lower extremity deep venous thrombosis, 0.8% versus 0.7% ($p=0.39$). Lower mortality was shown with pelvic vein deep venous thrombosis treated with thrombolytics than with anticoagulants, 0% versus 0.8% ($p<0.0001$). In-hospital pulmonary embolism occurred in 11% to 23%, irrespective of the site of deep venous thrombosis.

CONCLUSION: Patients with deep venous thrombosis involving the inferior vena cava had higher in-hospital mortality than patients with deep venous thrombosis at other locations. Pelvic vein deep venous thrombosis did not result in higher mortality or more in-hospital pulmonary embolism than proximal lower extremity deep venous thrombosis. The incidence of in-hospital pulmonary embolism was considerable with deep venous thrombosis at all sites.

© 2020 Elsevier Inc. All rights reserved. • *The American Journal of Medicine (2020) 000:1−5*

KEYWORDS: Deep venous thrombosis; Pulmonary embolism; Thrombolytic therapy; Venous thromboembolism

Proximal (popliteal vein or proximally) deep venous thrombosis requires treatment with anticoagulants.[1] Isolated distal deep venous thrombosis can be managed with serial imaging to detect extension of the thrombus or it can be managed with anticoagulants.[1] In-hospital mortality for deep venous thrombosis involving the inferior vena cava and for noncaval deep venous thrombosis in 1 investigation was similar.[2] Mortality at 3 months[3] and at 12 months[4] has been described for lower extremity deep venous thrombosis, either proximal or distal. However, there is a lack of subgroup analyses in published trials focused on iliofemoral deep venous thrombosis.[5] Such subgroup analysis may be important; patients with iliofemoral vein thrombosis had a 2.4-fold increased risk of recurrent venous thromboembolism over 3 months of follow-up compared with patients with less extensive deep venous thrombosis.[6] Separate reporting of iliofemoral deep venous thrombosis outcome, therefore, has been encouraged.[5] In the present investigation we assess in-hospital mortality of deep venous thrombosis involving the inferior vena cava, pelvic veins, proximal veins of the lower extremities, and distal veins of the lower extremities. We also evaluate the use of thrombolytic therapy and anticoagulants in these groups.

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Paul D. Stein, MD, Michigan State University, College of Osteopathic Medicine, Department of Osteopathic Medical Specialties, 909 Wilson Road, B 305 West Fee, East Lansing, MI 48824.

E-mail address: steinp@msu.edu

0002-9343/© 2020 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjmed.2020.11.013

METHODS

This was a retrospective cohort study based on administrative data from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, 2016 and 2017.[7] The Nationwide Inpatient Sample in 2016 and 2017 was a sample of discharge records from all US non-Federal, short-term, general, and other specialty hospitals participating in the Healthcare Cost and Utilization Project.[7] Weighted estimates of the number of hospitalizations with a discharge diagnosis of deep venous thrombosis were used. This investigation was determined by the institutional review board not to meet the definition of "human subjects" because the database includes only de-identified patients.

Patients were identified by International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM) Codes (Table 1). The ICD-10-CM for introduction of a thrombolytic agent into a peripheral vein does not distinguish between intravenous systemic thrombolytic therapy and thrombolytic therapy injected directly into a thrombosed vein. We deleted patients who had thrombolytic agents injected into a central artery, which would have been administered for pulmonary embolism.

Included patients were adults (aged ≥ 18 years) of both genders and all races hospitalized in short-stay hospitals in all regions of the United States with a primary (first-listed) diagnosis of deep venous thrombosis at identified locations. We deleted patients who had deep venous thrombosis at unspecified locations. We stratified patients according to whether they had deep venous thrombosis at the following sites: inferior vena cava, pelvic veins including the iliac veins, proximal deep veins of the lower extremities including the femoral and popliteal veins, and distal lower extremity including the tibial veins.

CLINICAL SIGNIFICANCE

- Patients with deep venous thrombosis involving the inferior vena cava had higher in-hospital mortality than patients with deep venous thrombosis at other locations.
- Pelvic vein deep venous thrombosis was not associated with higher in-hospital mortality than proximal lower extremity deep venous thrombosis.
- Pelvic vein deep venous thrombosis was not associated with higher prevalence of in-hospital pulmonary embolism than proximal lower extremity deep venous thrombosis.
- In-hospital pulmonary embolism was frequent with deep venous thrombosis at all sites.

Mortality with thrombolytic therapy was determined in patients with deep venous thrombosis at each site. In all instances, "mortality" refers to in-hospital all-cause mortality (case fatality rate). Adverse effects including intracerebral hemorrhage were assessed with thrombolytic therapy.

We assumed that patients were treated with anticoagulants if they did not receive thrombolytic therapy. We assumed that patients who received thrombolytic therapy received anticoagulants in addition.

Differences between categorical variables were calculated with the 2-tailed Fisher's exact test using MedCalc statistical software (Osland, Belgium). Continuous variables were expressed as mean ± standard deviation and were calculated using Graphpad QuickCalcs, Graphpad (San Diego, Calif). The 95% confidence intervals (CIs) were calculated with the modified Wald method using Graphpad QuickCalcs. A P value ≤ .05 was considered statistically significant. Number needed to treat, and absolute risk reduction with their 95% CIs were calculated using Graphpad QuickCalcs.

Table 1 International Classification of Diseases, 10th Revision, Clinical Modification Codes Used

Condition	ICD-10-CM Code
Acute DVT distal lower extremity	I82.4Z,I82.4Z1, I82.4Z2, I82.4Z3, I82.4Z9, I82.441,I82.442, I82.443, I82.449,
Acute DVT proximal lower extremity	I82.431, I82.432, I82.433, I82.439,I82.4Y, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Y9, I82.41, I82.411, I82.412, I82.413, I82.419
Acute DVT pelvic vein	I82.421, I82.422,I82.423, I82.429, I82.890
Acute DVT inferior vena cava	I82.220
Acute DVT unspecified of lower extremity	I82.40, I82.401,I82.402, I82.403, I82.49, I82.491, I82.492, I82.493, I82.499
Acute DVT unspecified lower extremity postpartum	I82.409
Pulmonary embolism	I26.92, I26.99, I26.02, I26.09
Introduction of thrombolytic into central artery, percutaneous approach	3E06317
Introduction of thrombolytic into peripheral vein, percutaneous approach	3E03317
Adverse effects of thrombolytic drugs	T45.615A
Intracerebral hemorrhage	I61

DVT = deep venous thrombosis; ICD-10-CM = International Classification of Diseases, 10th revision, Clinical Modification Codes.

ARTICLE IN PRESS

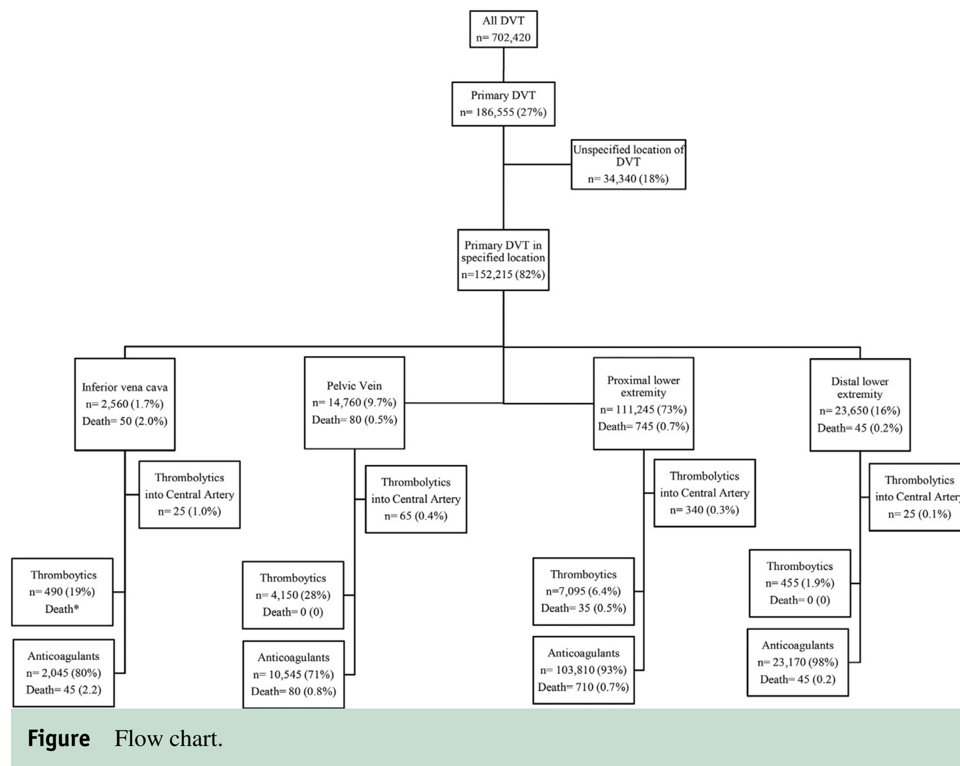

Figure Flow chart.

RESULTS

In 2016 and 2017, 152,215 patients were hospitalized in the United States with a primary diagnosis of acute deep venous thrombosis at identified locations. Thrombus locations were the inferior vena cava 1.7%, pelvic vein 9.7%, proximal lower extremity 73.1%, and distal lower extremity 15.5% (Figure). Demographic characteristics are shown in Table 2.

Mortality in patients treated with anticoagulants who had deep venous thrombosis involving the inferior vena cava was higher than mortality with deep venous thrombosis in the pelvic veins (2.2% compared with 0.8%; $P < .0001$; Table 3). Mortality with deep venous thrombosis involving the inferior vena cava was also higher than mortality with proximal or distal lower extremity deep venous thrombosis (Table 3). Mortality in patients treated only with anticoagulants was similar in patients with pelvic vein deep venous thrombosis and proximal lower extremity deep venous thrombosis (Table 3, Figure). Patients with distal lower extremity deep venous thrombosis treated with antigoagulants only, had lower mortality than patients with pelvic vein deep venous thrombosis or proximal lower extremity deep venous thrombosis (Table 3, Figure).

A larger proportion of patients with pelvic vein deep venous thrombosis received thrombolytic therapy than patients with inferior vena cava thrombosis (28% compared with 19%; $P < .0001$; Figure). A larger proportion of patients with pelvic vein deep venous thrombosis or inferior vena cava thrombosis received thrombolytic therapy than patients with proximal lower extremity deep venous

Table 2 Demographic Characteristics According to Location of Deep Venous Thrombosis*

	Distal Lower Extremity	Proximal Lower Extremity	Pelvic Vein	Inferior Vena Cava
Age, years (mean ± SD)†	64 ± 17	65 ± 17	59 ± 18	55 ± 18
Female n/N (%)	12,085/23,630 (51%)	55,120/111,175 (50%)	8.680/14.745 (59%)	1,275/2,555 (50%)
White n/N (%)	16,100/23,085 (70%)	75,515/108,245 (69%)	10,080/14,075 (72%)	1,720/2,445 (70%)
Black n/N (%)	4,010/23,085 (17%)	20,740/108,245 (19%)	2,195/14,075 (16%)	415/2,445 (17%)
Hispanic n/N (%)	2,000/23,085 (8.7%)	8,865/108,245 (8.2%)	1,150/14,075 (8.2%)	180/2,445 (7.4%)
Asian American n/N (%)	235/23,085 (1.0%)	955/108,245 (0.9%)	240/14,075 (1.7%)	60/2,445 (2.5%)
Native American n/N (%)	70/23,085 (0.3%)	400/108,245 (0.4%)	60/14,075 (0.6%)	25/2,445 (1.0%)

SD = standard deviation.
*Data were missing in some patients.
†Age $P < .0001$ distal lower extremity vs proximal lower extremity, distal lower extremity vs pelvic vein, pelvic vein vs inferior vena cava.

Table 3 Mortality According to Treatment and Location of Deep Venous Thrombosis

Location of Deep Venous Thrombosis	Mortality Anticoagulants n/N (%)	95% CI	Mortality Thrombolytics n/N (%)	95% CI	*P* Anticoagulants vs Thrombolytics
Distal lower extremity	45/23,170 (0.2%)	0.1%-0.3%	0/455 (0%)	0%-0.8%	.12
Proximal lower extremity	710/103,810 (0.7%)*	0.6%-0.7%	35/7,095 (0.5%)	0.4%-0.7%	.06
Pelvic vein	80/10,545 (0.8)†,‡	0.6%-0.9%	0/4,150 (0%)	0%-0.1%	<.0001
Inferior vena cava	45/2,045 (2.2%)§	1.7%-2.9%	#/490	-	-

CI = confidence interval.#Insufficient data
**P* < .0001 proximal lower extremity vs distal lower extremity.
†P = .39 pelvic vein vs proximal lower extremity.
‡P < .0001 pelvic vein vs distal lower extremity.
§P < .0001 inferior vena cava vs pelvic vein, inferior vena cava vs proximal lower extremity, inferior vena cava vs distal lower extremity.

thrombosis or distal lower extremity deep venous thrombosis (19% and 28% compared with 6.4% and 1.9%; $P <$ .0001; Figure).

Lower mortality was shown in patients with pelvic vein deep venous thrombosis treated with thrombolytic agents than with anticoagulants (Table 3). The absolute risk reduction was 0.8% (95% CI, 0.6%-0.9%). The number needed to treat was 132 (95% CI, 108-169). In the distal and proximal lower extremities, mortality was not significantly lower with thrombolytic therapy than with anticoagulants. Adverse events were reported in 115 of 12,190 (0.9%) patients who received thrombolytic therapy. No deaths and no intracerebral hemorrhages resulted from thrombolytic therapy.

In-hospital pulmonary embolism occurred in 11% to 23% of patients with deep venous thrombosis, irrespective of the site (Table 4). Counterintuitively, a lower proportion of patients with deep venous thrombosis involving the inferior vena cava or pelvic vein had pulmonary embolism diagnosed in-hospital than patients with proximal or distal lower extremity deep venous thrombosis.

DISCUSSION

In-hospital all-cause mortality was higher in patients with inferior vena cava thrombosis treated with anticoagulants than in patients with deep venous thrombosis at other locations. Mortality on anticoagulants was similar in patients with pelvic vein deep venous thrombosis and proximal lower extremity deep venous thrombosis. Patients with distal lower extremity deep venous thrombosis had lower mortality. Mortality was lower in patients with pelvic vein deep venous thrombosis treated with thrombolytic agents than with anticoagulants, but this was balanced by adverse events. The incidence of in-hospital pulmonary embolism was not higher in patients with inferior vena cava or pelvic vein deep venous thrombosis than in patients with proximal or distal lower extremity deep venous thrombosis. The incidence of in-hospital pulmonary embolism was considerable with deep venous thrombosis at all sites.

Table 4 In-Hospital Pulmonary Embolism According to Location of Deep Venous Thrombosis*

Location of Deep Venous Thrombosis	In-hospital Pulmonary Embolism n/N (%)†
Distal lower extremity	5,445/23,650 (23%)
Proximal lower extremity	24,640/111,245 (22%)
Pelvic vein	2,470/14,760 (17%)
Inferior vena cava	275/2,560 (11%)

**P* = .003 proximal lower extremity vs distal lower extremity.
†*P* < .0001 inferior vena cava vs pelvic vein, pelvic vein vs proximal lower extremity.

We assume that if a patient had both pulmonary embolism and deep venous thrombosis on admission, the primary diagnosis would have been pulmonary embolism, which is the more serious. Any discharge code for pulmonary embolism, therefore, indicated that pulmonary embolism was diagnosed during hospitalization. Even though pulmonary embolism was not recognized on admission, we cannot be sure that pulmonary embolism developed in-hospital in all patients with a secondary diagnosis of pulmonary embolism. Some patients with deep venous thrombosis might have had silent pulmonary embolism on admission. Silent pulmonary embolism, based on review of prospective investigations, occurred in 31% of patients with deep venous thrombosis[8] and it occurred in 66% of patients with deep venous thrombosis in 1 investigation.[9] Silent pulmonary embolism may involve central pulmonary arteries[10] and involve over 60% of the pulmonary circulation.[11]

Post-thrombotic syndrome has been reported to be lower in patients treated with catheter-directed thrombolysis.[12,13] However, results are not uniform. A randomized controlled trial of 692 patients with femoral, common femoral, or iliac vein deep venous thrombosis showed that catheter-directed thrombolysis did not result in a lower rate of post−thrombotic syndrome after 24 months.[14] Recurrent venous thromboembolism over a 24-month period was not lower in patients who received catheter-directed thrombolysis.[12,14]

A strength of this investigation is that it is the only investigation that evaluates deep venous thrombosis in hospitalized patients according to whether the thrombus is in pelvic veins compared with proximal or distal veins of the lower extremity. Weaknesses include lack of follow-up. We do not know if patients treated with thrombolytic agents had a lower incidence of post-thrombotic syndrome than patients

ARTICLE IN PRESS

treated with anticoagulants. We do not know if thrombolytic therapy reduced the incidence of recurrent pulmonary embolism. Also, we do not know if thrombolytic therapy was administered systemically or directly into a thrombosed vein. We do not know the positive predictive value of ICD-10-CM codes used in the present investigation. The **Positive predictive value of the** ICD-9-CM codes for proximal or distal deep venous thrombosis in the principal position were 95%.[15]

In conclusion, patients with deep venous thrombosis involving the inferior vena cava had higher in-hospital mortality than patients with deep venous thrombosis at other locations. Pelvic vein deep venous thrombosis did not have higher in-hospital mortality than proximal lower extremity deep venous thrombosis, and it was not associated with higher rate of pulmonary embolism diagnosed in-hospital. In-hospital pulmonary embolism was frequent with deep venous thrombosis at all sites.

References

1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016; 149:315–52.
2. 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.
3. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;279:458–62.
4. Cohen AT, Gitt AK, Bauersachs R, et al. Prefer In Vte Scientific Steering Committee And The Prefer In Vte Investigators OBOT. The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE Registry. *Thromb Haemost* 2017;117:1326–37.
5. Jaff MR, McMurtry MS, Archer SL, et al. American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123: 1788–830.
6. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? *Am J Med* 2001;110:515–9.
7. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Available at: https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp. Accessed June 8, 2020.
8. Stein PD, Matta F, Musani MH, Diaczok B. Silent pulmonary embolism in patients with deep venous thrombosis: a systematic review. *Am J Med* 2010;123:426–31.
9. López-Beret P, Pinto JM, Romero A, Orgaz A, Fontcuberta J, Oblas M. Systematic study of occult pulmonary thromboembolism in patients with deep venous thrombosis. *J Vasc Surg* 2001;33:515–21.
10. Hirsch JF, Demilly P. Screening of asymptomatic pulmonary embolisms by systematic scintigraphy in apparently uncomplicated phlebitis. *Ann Med Interne (Paris)* 1991;142:168–70.
11. García-Fuster MJ, Fabia MJ, Furió E, et al. Should we look for silent pulmonary embolism in patients with deep venous thrombosis? *BMC Cardiovasc Disord* 2014;14:178. https://doi.org/10.1186/1471-2261-14-178.
12. Enden T, Haig Y, Kløw NE, et al. CaVenT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet* 2012;379:31–8.
13. Haig Y, Enden T, Grøtta O, et al. CaVenT Study Group. 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 [e64-e71.
14. Vedantham S, Goldhaber SZ, Julian JA, et al. ATTRACT Trial Investigators. Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis. *N Engl J Med* 2017;377:2240–52.
15. White RH, Garcia M, Sadeghi B, et al. Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. *Thromb Res* 2010;126:61–7.