Meta-analysis and systematic review of interventional therapy versus anticoagulation for isolated femoropopliteal deep venous thrombosis

Gregory Eckenrode, MD,[a] Becky Baltich Nelson, MLS,[b] Andre Belarmino, BA,[a] Stephanie Ashley Chen, BA,[a] Shokhi Goel, BA,[a] *and* Andrew J. Meltzer, MD,[c] *New York; and Phoenix, Ariz*

ABSTRACT

Objective: Percutaneous endovenous intervention (PEVI) is gaining acceptance for select patients with symptomatic proximal lower extremity deep venous thrombosis (DVT), but the benefits are uncertain in patients with isolated femoropopliteal DVTs. We performed a systematic review and meta-analysis of the literature to assess the safety and effectiveness of PEVI vs systemic anticoagulation for patients with isolated femoropopliteal DVT.

Methods: We systematically searched PubMed, Embase, and the Cochrane Library from inception to March 2018. All studies comparing clinical outcomes between PEVI and systemic anticoagulation were included. The main end points were post-thrombotic syndrome and bleeding complications. Secondary outcomes included femoropopliteal patency rate, venous obstruction, and recurrent DVT.

Results: No studies directly comparing PEVI with systemic anticoagulation in isolated femoropopliteal DVTs were identified by the systematic review. A traditional literature review identified one randomized controlled trial comparing the two, which found no difference in rates of post-thrombotic syndrome in PEVI vs systemic anticoagulation (risk ratio, 0.96; 95% confidence interval, 0.82-1.11; $P = .56$). We additionally identified five retrospective case series containing patients with isolated femoropopliteal DVTs, of which two reported on patency rates (46%-100% at 2 years).

Conclusions: More data are required to definitively state that PEVI should be the preferred intervention for patients with isolated femoropopliteal DVTs, although the initial evidence is promising. (J Vasc Surg: Venous and Lym Dis 2018;■:1-5.)

Keywords: Venous thrombosis; Thrombectomy; Angioplasty; Anticoagulants; Antithrombins

Lower extremity deep venous thrombosis (DVT) is associated with numerous adverse outcomes, of which pulmonary embolism is the most serious. Historically, the preferred treatment of DVT was limited to systemic anticoagulation. Although it is effective in preventing the dreaded complication of pulmonary embolism, systemic anticoagulation does not immediately clear the clot burden, leaving the patient at risk for long-term sequelae, including chronic venous insufficiency and post-thrombotic syndrome (PTS).[1] These long-term complications are more prevalent in patients with extensive iliofemoral DVTs.[2,3] As a result, percutaneous endovenous interventions (PEVIs) including catheter-directed thrombolysis, pharmacomechanical thrombectomy (PMT), and other techniques have been primarily evaluated in this population. For patients with proximal iliofemoral DVT, PEVI has gained acceptance as a means to immediately reduce or to eliminate clot burden and restore venous flow, ultimately reducing rates of PTS.[4] Many practitioners now recommend PEVI for selected patients with iliofemoral DVT.[5] Although patients with DVT confined to the femoropopliteal segments are also at risk for PTS,[6] the role of PEVI in patients with DVT isolated to the infrainguinal deep veins has not been defined.[7]

The objective of this systematic review, therefore, was to compare systemic anticoagulation with PEVI in adult patients with isolated femoropopliteal DVT. The outcome measures were treatment effectiveness, rate and severity of complications, rates of rethrombosis, PTS, and other sequelae. Pediatric patients and women who were pregnant were excluded because of a markedly different procedural risk profile. All other patients were included.

METHODS

Search strategy. The study was registered into PROSPERO, the international prospective register of systematic reviews (registration No. CRD42018089785) and followed the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[8]

A comprehensive literature search was conducted by a medical librarian on March 19, 2018, using the following bibliographic databases from inception: Ovid MEDLINE

From the Department of Surgery,[a] Information Technologies and Services — Library,[b] Weill Cornell Medical College, New York; and the Department of Vascular and Endovascular Surgery, Mayo Clinic, Phoenix.[c]

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Correspondence: Gregory Eckenrode, MD, Weill Cornell Medical Center, 525 E 68th St, New York, NY 10021 (e-mail: gje9002@nyp.org).

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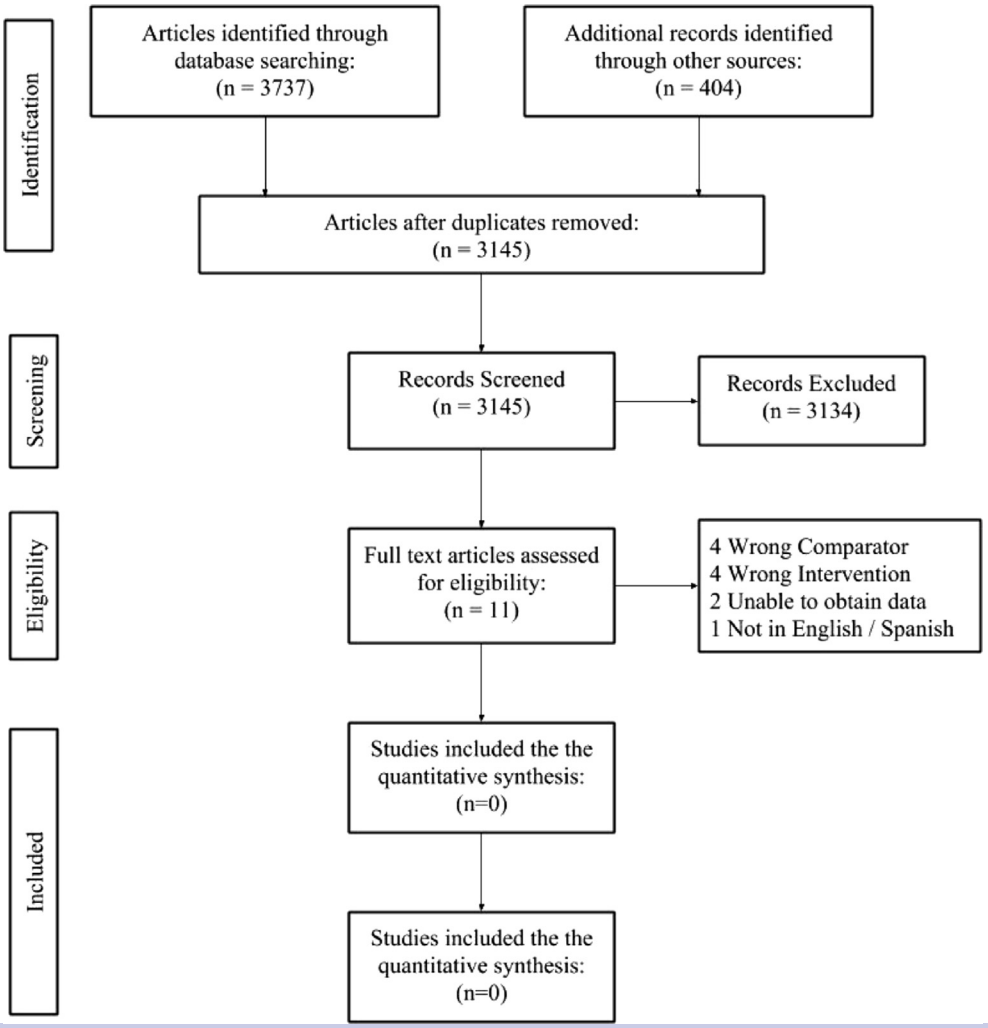

Fig. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for the progress of articles through the selection process. Reasons for inclusion and exclusion are as indicated.

(In-Process & Other Non-Indexed Citations and Ovid MEDLINE 1946 to Present); Ovid EMBASE (1974 to present); and The Cochrane Library (Wiley). No language, publication date, or article type restrictions were included in the search (Supplementary Table, online only).

Study selection. The 3737 results produced from the database searches were imported into Covidence, a systematic review screening tool, and de-duplicated. The remaining 2922 citations were screened by title and abstract against predetermined inclusion and exclusion criteria by two independent reviewers, with a third reviewer resolving discrepancies. To be eligible, articles had to meet the following inclusion criteria: studies of isolated infrainguinal femoropopliteal DVTs; and systemic anticoagulation vs percutaneous endovascular procedure. Exclusion criteria included case studies and series, articles in a language other than English, studies whose patients were either pregnant or pediatric patients, studies in which the intervention was an inferior vena cava filter, and iliac or iliofemoral clots.

Eleven articles were selected for full-text review. Both reference and relevant article lists for these articles were gathered and de-duplicated, producing 223 additional citations for review; however, none of these were selected for further screening. From the full-text review, none of the 11 articles met inclusion criteria for this study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram outlines the study selection process (Fig).

RESULTS

Results of individual studies. Whereas many studies have compared procedural intervention with systemic anticoagulation in the treatment of iliofemoral DVT, the search of comparable trials addressing infrainguinal venous disease yielded no results. Therefore, a traditional literature review was performed to assess for any articles reporting on procedural intervention for femoropopliteal

Table. Publications reporting on percutaneous endovenous intervention (*PEVI*) for isolated femoropopliteal deep venous thrombosis (*DVT*)

Authors	Year	Patients	Femoropopliteal patients	PTS		Patency	Lysis grade[a]	Valvular competence
				PEVI	Anticoagulation			
Randomized controlled trial								
Vedantham et al	2017	692	294	59/135 (44%)	70/159 (44%)	NA	NA	NA
Retrospective case series								
Stanley et al	2013	80	17	NA	NA	100% at 6 months 100% at 3.8 years	NA	70% at 3.8 years in acute DVT 14.3% at 3.8 years for chronic DVT
Mewissen et al	1999	302	79	NA	NA	46.8%-63.6% at 12 months, depending on chronicity	I: 4 (20%) II: 39 (49%) III: 24 (30%)	NA
Bozkurt et al	2015	14	5	NA	NA	NA	NA	NA
Köksoy et al	2014	42	16	NA	NA	NA	NA	NA
Ozpak et al	2016	21	9	NA	NA	NA	NA	NA

NA, Not applicable; *PTS*, post-thrombotic syndrome.
Outcomes specific to PEVI in isolated femoropopliteal DVT are shown as reported.
[a]Lysis grades are defined as follows: grade I, lysis of <50% of the clot; grade II, lysis of 50% to 99% of the clot; grade III, lysis of 100% of the clot.

DVTs with or without comparison to systemic anticoagulation. This search revealed one randomized controlled trial (the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis [ATTRACT] trial)[6] and five retrospective case series of patients who had undergone percutaneous intervention for lower extremity DVTs that included patients with isolated femoropopliteal DVTs.[9-13] Of these five studies, three reported aggregate data for all study participants and did not separately report data for patients with isolated femoropopliteal DVTs. One study (Stanley et al[9]) separately reported patency rates and valve function rates, and one study (Mewissen et al[10]) separately reported author-defined lysis grades.

The ATTRACT trial was a multicenter, randomized controlled clinical trial comparing PMT with systemic anticoagulation for patients with acute lower extremity DVT with the primary outcome of PTS between 6 and 24 months of follow-up. There were 692 patients randomized to anticoagulation alone (control group) or to anticoagulation plus pharmacomechanical thrombolysis between 2009 and 2014. The overall results of this study were no difference between groups for rates of all PTS (47% in the PMT group vs 48% in the control group; risk ratio, 0.96; 95% confidence interval [CI], 0.82-1.11; $P = .56$), rates of recurrent venous thromboembolism (12% in the PMT and 8% in the control group; $P = .09$), or improvement of quality of life. It found significant differences in rates of major bleeding events within 10 days (1.7% in the PMT group vs 0.3% in the control group; $P = .049$); moderate to severe PTS (18% in the PMT group vs 24% in the control group; risk ratio, 0.73; 95% CI, 0.54-0.98; $P = .04$); and Villalta scores at 6-, 12-, 18-, and 24-month follow-up points ($P < .01$ at each point). A subgroup analysis was performed of patients with isolated acute femoropopliteal DVTs. The study included 294 patients with femoropopliteal DVTs, of whom 135 were randomized to procedural intervention and 159 were randomized to systemic anticoagulation. There was no significant difference in rates of overall PTS between groups (44% in both groups; adjusted risk ratio, 0.94; 95% CI, 0.81-1.10; $P = .47$). Data for major bleeding events, deaths, moderate to severe PTS, Villalta scores, and patency rates were not separately reported for isolated femoropopliteal DVT patients.

The results of the cohort studies are summarized in the Table. The studies were published between 1999 and 2016. Stanley et al reported in 2013 on a case series of 80 patients, 17 of whom had femoropopliteal DVTs. They reported 6-month and 3.8-year (mean follow-up) patency rates of 100% for both acute and chronic DVTs. At the end of follow-up, valve function rate was 75% for acute DVTs and 14.3% for chronic DVTs.

Mewissen et al reported a case series of 302 patients that included 79 with femoral-popliteal DVTs. They reported a lysis grade, defined by the authors as follows: grade I, lysis of <50% of the clot; grade II, lysis of 50% to 99% of the clot; and grade III, complete lysis of the clot as determined by X-ray venography. This study found lysis grade I for 16 (20%), grade II for 39 (49%), and grade III

for 24 (30%) of these patients and a 12-month primary patency rate of 46.8% to 63.6%, depending on the chronicity of the clot. No study separately reported complication rates for femoropopliteal DVT patients.

Synthesis of results. Combined, these results indicate that procedural intervention is effective at rapidly clearing femoropopliteal clots with patency rates between 46.8% and 100% at up to 3.8 years of follow-up. Direct comparison between procedural intervention and systemic anticoagulation was performed in only one study, which showed no difference in rates of PTS between the two treatments. No study separately compared the rates of complications between systemic anticoagulation and femoropopliteal DVTs.

DISCUSSION

Summary of evidence. The evidence from multiple randomized controlled trials of PEVI vs systemic anticoagulation for iliofemoral DVT treatment shows a benefit in reducing PTS through the use of procedural interventions at the cost of an increased rate of bleeding.[4] Only one of these trials separately reported data for femoropopliteal DVTs, which makes evidence for the utility of percutaneous chemical thrombectomy and PMT in femoropopliteal DVTs much more limited. This is despite the fact that these patients also experience a high rate of PTS, as in the ATTRACT trial, in which nearly half of patients developed PTS during a 2-year period. This high prevalence of PTS is the result of the limitations of endogenous lytic mechanisms, which are often inadequate in the face of a substantial clot burden.[14]

The available evidence suggests that current interventional techniques are effective at removing clot, restoring flow, and maintaining patency in the intermediate term. This has led some professional societies, such as the Society of Interventional Radiology,[15] the American Heart Association (AHA),[3] and the Society for Vascular Surgery (SVS),[16] and the Interdisciplinary Expert Panel on Iliofemoral Deep Vein Thrombosis[17] to recommend the use of percutaneous endovascular intervention in select patients with symptomatic DVTs. These societies all recommend PEVI in situations in which the patient has phlegmasia cerulea dolens or the limb is otherwise threatened; the AHA and the SVS even recommend transfer to a facility that can offer PEVI if the diagnosing facility is unable to provide this service. The Society of Interventional Radiology, AHA, and SVS additionally recommend PEVI for early clot removal in selected patients with iliofemoral DVT. In contrast, the CHEST guidelines for management of DVT[18] recommend systemic anticoagulation over PEVI. This variance in society guidelines is reflective of both the limited, variable nature of the data supporting the use of PEVI and the gradual acceptance of PEVI by large national organizations as the preferred treatment modality.[19] Whereas the role of PEVI in the treatment of proximal DVT continues to expand, data are currently insufficient to definitively state that procedural intervention significantly improves rates of PTS in patients with femoropopliteal DVT compared with anticoagulation alone. This lack of data was noted by the SVS, which recommend against the use of PEVI in isolated femoropopliteal DVTs at present while strongly encouraging continued investigation into the matter. This highlights the need for additional studies to examine the potential benefits of PEVI for patients with isolated femoropopliteal DVTs.

Limitations. This systematic review is limited primarily by the paucity of data regarding interventional therapy for femoropopliteal DVTs as well as limited reporting of long-term outcomes and complications related to procedural interventions. In addition, this search strategy did not identify the ATTRACT trial as a potential article despite reporting data specifically about patients with isolated femoropopliteal DVTs. This is because femoropopliteal outcomes were reported in supplemental material rather than in the body of the article, and keyword and abstract screen did not identify the article. Therefore, it is possible that other studies with supplemental reporting were similarly missed by the search strategy, although none of the four previous randomized controlled trials reported data for femoropopliteal patients.

CONCLUSIONS

Despite multiple large trials focusing on iliofemoral DVT, this broad systematic review found no published evidence directly comparing procedural intervention with systemic anticoagulation for femoropopliteal DVTs. A traditional literature search uncovered a single randomized controlled trial that compared these two treatments in a limited supplemental analysis and found no difference in rates of PTS without reporting on complications or other outcomes. Several case series found that procedural intervention on femoropopliteal DVTs resulted in excellent rates of patency for as long as 3.8 years. Clearly, more data are needed to assess the effectiveness and safety of procedural intervention for these patients. It is currently unknown whether PEVI is superior to systemic anticoagulation for the treatment of isolated femoral DVTs.

AUTHOR CONTRIBUTIONS

Conception and design: GE, BN, AM
Analysis and interpretation: GE, BN, AB, SC, AM
Data collection: GE, BN, AB, SC, SG, AM
Writing the article: GE, BN, AM
Critical revision of the article: GE, BN, AB, SC, SG, AM
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