JAMA Clinical Evidence Synopsis

Treatment of Lower Extremity Superficial Thrombophlebitis

Marcello Di Nisio, MD, PhD; Saskia Middeldorp, MD, PhD

CLINICAL QUESTION What treatments for lower extremity superficial thrombophlebitis are associated with lower rates of venous thromboembolic events (VTE), major bleeding, and superficial venous thrombosis extension?

BOTTOM LINE Fondaparinux (2.5 mg) subcutaneously once daily for 45 days is associated with fewer symptomatic VTEs and lower rates of superficial venous thrombosis extension and recurrence with no increases in major bleeding compared with placebo. Low-molecular-weight heparin and nonsteroidal anti-inflammatory drugs are associated with lower rates of superficial thrombophlebitis extension or recurrence, but data regarding symptomatic VTEs are inconclusive.

Superficial thrombophlebitis recurs, extends, or progresses to venous thromboembolism in 10% of patients despite treatment.[1] The primary goal of treating superficial thrombophlebitis is preventing these complications and improving local symptoms and signs.[1,2] This JAMA Clinical Evidence Synopsis summarizes the efficacy and safety of parenteral, oral, topical, and surgical treatments for superficial thrombophlebitis.

Summary of Findings

One large, double-blind, placebo-controlled randomized clinical trial of 3002 low-risk patients with acute symptomatic superficial thrombophlebitis showed that fondaparinux (2.5 mg) once daily subcutaneously for 45 days was associated with lower rates of symptomatic venous thromboembolic events (VTEs) (3 of 1502 patients taking fondaparinux vs 20 of 1500 patients taking placebo; relative risk [RR], 0.15 [95% CI, 0.04-0.50]; number needed to treat, 88), superficial thrombophlebitis extension (4 of 1502 patients taking fondaparinux vs 51 of 1500 patients taking placebo; RR, 0.08 [95% CI, 0.03-0.22]), and recurrence (5 of 1502 patients taking fondaparinux vs 24 of 1500 patients taking placebo; RR, 0.21 [95% CI, 0.08-0.54]), with comparable rates of major bleeding (0.1% in both groups).[3]

In 1 study, low-molecular-weight heparin (LMWH) was associated with lower rates of superficial thrombophlebitis extension or recurrence at both prophylactic (37 of 112 patients taking placebo vs 16 of 110 patients taking LMWH; RR, 0.44 [95% CI, 0.26-0.74]) and therapeutic doses (16 of 106 patients taking LMWH; RR, 0.46 [95% CI, 0.27-0.77]) compared with placebo, with no differences in symptomatic VTEs or major bleeding.[4]

Head-to-head comparisons suggested that 30-day intermediate doses or therapeutic doses of LMWH were associated with lower VTE event rates than shorter courses of intermediate doses or lower doses of LMWH with no increases in major bleeding (**Table**).[5,6] There was insufficient evidence to establish an association of LMWH with benefit or harm compared with topical heparin gel, nonsteroidal anti-inflammatory drugs (NSAIDs), or surgical therapy.

NSAIDs were associated with lower rates of superficial thrombophlebitis extension and/or recurrence compared with placebo (15 of 99 patients taking NSAIDs vs 37 of 112 taking placebo; RR, 0.46 [95% CI, 0.27-0.78]). There was no association of NSAIDs with reductions in VTEs (4 of 99 patients taking NSAIDs vs 5 of 112 taking placebo; RR, 0.91 [95% CI, 0.25-3.28]).[4]

Nine trials reported no associations of topical treatment on VTEs or superficial thrombophlebitis extension or recurrence. Three studies on surgical treatment (saphenofemoral disconnection, thrombectomy, and venous stripping) and 8 studies on oral (vasotonin, heparan sulfate, sulodexide, oxyphenbutazone, vitamin K-antagonists, and oxerutins), intramuscular (desmin), or intravenous (enzyme) treatment were inconclusive due to small sample size, low quality, and poor reporting.[4]

Discussion

Based on 1 trial, fondaparinux (2.5 mg) subcutaneously once daily for 45 days is associated with lower rates of VTEs and superficial thrombophlebitis extension and recurrence compared with placebo, with no increases in major bleeding. Low-molecular-weight heparin and NSAIDs are associated with lower rates of extension or recurrence of superficial thrombophlebitis, but data regarding symptomatic VTEs are inconclusive.

Evidence Profile

No. of randomized clinical trials: 30

Study years: Published, 1970-2012

No. of patients: 6462

Men: 2115 **Women:** 3746; sex not reported, 6 studies

Race/Ethnicity: Unavailable

Age, range: 19 to 94 years; not reported, 3 studies

Settings: Outpatients, 7 studies; outpatients and inpatients, 4 studies; not reported, 19 studies

Countries: Austria, Bulgaria, Czech Republic, Estonia, France, Germany, Greece, Hungary, Israel, Italy, Latvia, the Netherlands, Poland, Russia, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, United States

Comparison: Topical treatments, compression stockings or bandages, medical treatments, and surgery; interventions could be compared with each other, placebo, or no intervention; combinations of therapies could be used

Primary outcomes: Efficacy: symptomatic VTE (ie, deep vein thrombosis [DVT] and pulmonary embolism [PE]); safety: major bleeding

Secondary outcomes: Symptomatic PE; symptomatic DVT or progression of superficial thrombophlebitis to DVT; extension or recurrence of superficial thrombophlebitis; symptoms and signs; quality of life; mortality; treatment adverse effects; arterial thromboembolic events

Table. Venous Thromboembolism in Studies Evaluating Low-Molecular-Weight Heparin for the Treatment of Superficial Thrombophlebitis

Source	Type of LMWH and Dose	Control	VTE, No. of Events/ No. of Patients		RR (95% CI)[a]
			LMWH Group	Control Group	
Stenox, 2003	Enoxaparin, 40 mg sc once daily	Placebo	6/110	5/112	1.22 (0.38-3.89)
	Enoxaparin, 1.5 mg/kg sc once daily	Placebo	4/106	5/112	0.85 (0.23-3.06)
Cosmi, 2012	Parnaparin, 8500 IU sc once daily for 10 d followed by 6400 IU sc once daily for 20 d	Parnaparin, 4250 IU sc once daily for 30 d	4/219	7/217	0.57 (0.17-1.91)
	Parnaparin, 4250 IU sc once daily for 30 d	Parnaparin, 8500 IU sc once daily for 10 d	7/217	11/212	0.62 (0.25-1.57)
	Parnaparin, 8500 IU sc once daily for 10 d followed by 6400 IU once daily for 20 d	Parnaparin, 8500 IU sc once daily for 10 d	4/219	11/212	0.35 (0.11-1.09)
Vesalio, 2005	Therapeutic weight-adjusted nadroparin for 10 d followed by half dose for 20 d[c]	Nadroparin, 2850 IU sc once daily	2/81	4/83	0.51 (0.10-2.72)
Gorski, 2005[b]	Enoxaparin, 40 mg sc once daily	Heparin spray gel	1/23	3/21	0.30 (0.03-2.70)
Katzenschlager, 2003[b]	Enoxaparin, 40 mg sc once daily	Heparin spray gel	0/21	0/18	
Stenox, 2003	Enoxaparin, 40 mg sc once daily	Tenoxicam, 20 mg once daily	6/110	4/99	1.35 (0.39-4.64)
	Enoxaparin, 1.5 mg/kg sc once daily	Tenoxicam, 20 mg once daily	4/106	4/99	0.93 (0.24-3.63)
Titon, 1994	Nadroparin, 6150 IU sc once daily	Naproxen, 500 mg once daily	0/38	0/35	
	Nadroparin, 61.5 IU/kg sc once daily	Naproxen, 500 mg once daily	0/36	0/35	
Lozano, 2003	Enoxaparin, 1mg/kg sc twice daily for the first wk, then 1 mg/kg for 3 wk	Saphenofemoral disconnection	0/30	2/30	0.20 (0.01-4.00)
Uncu, 2009	Ca-nadroparin, 190 IU/kg sc once daily	Ca-nadroparin, 190 IU/kg sc once daily + acemetacin, 60 mg twice daily	0/25	0/25	
Belcaro, 1999	Prophylactic LMWH + graduated compression stockings[d]	Graduated compression stockings	0/76	6/78	0.08 (0.00-1.38)

Abbreviations: LMWH, low-molecular-weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk; sc, subcutaneously. VTE, venous thromboembolic event (includes deep vein thrombosis and pulmonary embolism).

[a] The RR could not be estimated.

[b] The outcome reported is deep vein thrombosis.

[c] Patients weighing less than 50 kg received 0.4 mL of nadroparin (19 000 IU/mL) for 10 days, followed by 0.2 mL. Patients weighing 50 to 59 kg received 0.5 mL of nadroparin; 60 to 69 kg, 0.6 mL; 70 to 79 kg, 0.7 mL; 80 to 89 kg, 0.8 mL; and 90 kg or more, 0.9 mL; all followed by a half dose for an additional 20 days.

[d] Type and dose of LMWH not specified.

Limitations

Twelve of 30 studies compared an active treatment for superficial thrombophlebitis with placebo or no treatment. Of these 12, only 2 reported on VTEs or superficial thrombophlebitis extension or recurrence. Data were not available for separate analyses of high-risk vs low-risk patients. The data regarding fondaparinux are from 1 trial.

Comparison of Findings With Current Practice Guidelines

The present findings are partially consistent with the guidelines from the American College of Chest Physicians, which suggest a prophylactic dose of fondaparinux or LMWH for 45 days for superficial thrombophlebitis.[7] However, our review shows inconclusive results regarding the ability of LMWH to prevent VTEs compared with placebo.

Areas in Need of Future Study

Insufficient data are available on the use, dosage, and duration of LMWH, the role of oral NSAIDs, and of topical NSAIDs and compression stockings in combination with anticoagulant therapy. Fondaparinux for 45 days may not be cost-effective for isolated superficial thrombophlebitis.

ARTICLE INFORMATION

Author Affiliations: Department of Medical, Oral, and Biotechnological Sciences, Università "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy (Di Nisio); Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands (Di Nisio, Middeldorp).

Corresponding Author: Marcello Di Nisio, MD, PhD, Department of Medical, Oral, and Biotechnological Sciences, Università "G. D'Annunzio" of Chieti-Pescara, via dei Vestini 31, 66013 Chieti, Italy (mdinisio@unich.it).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Middeldorp reports serving as a member of the Steering Committee of the CALISTO study, which investigated the efficacy and safety of fondaparinux for superficial thrombophlebitis; consulting for Bayer, Boehringer, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, and Pfizer; receiving travel accommodations from GlaxoSmithKline; giving expert testimony for Court Netherlands; receiving grant funding from Bristol-Myers Squibb, Pfizer, and GlaxoSmithKline; and receiving payment for lectures from Boehringer, Bristol-Myers Squibb, and Pfizer. No other disclosures were reported.

REFERENCES

1. Decousus H, Quéré I, Presles E, et al. Superficial venous thrombosis and venous thromboembolism. *Ann Intern Med*. 2010;152(4):218-224.

2. Wichers IM, Di Nisio M, Büller HR, Middeldorp S. Treatment of superficial vein thrombosis to prevent deep vein thrombosis and pulmonary embolism. *Haematologica*. 2005;90(5):672-677.

3. Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363(13):1222-1232.

4. Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. *Cochrane Database Syst Rev*. 2013;4:CD004982.

5. Cosmi B, Filippini M, Tonti D, et al. A randomized double-blind study of low-molecular-weight heparin (parnaparin) for superficial vein thrombosis. *J Thromb Haemost*. 2012;10(6):1026-1035.

6. Prandoni P, Tormene D, Pesavento R; Vesalio Investigators Group. High vs. low doses of low-molecular-weight heparin for the treatment of superficial vein thrombosis of the legs. *J Thromb Haemost*. 2005;3(6):1152-1157.

7. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease. *Chest*. 2012;141(2 suppl):e419S-494S.