JAMA Clinical Evidence Synopsis

Treatment of Lower Extremity Superficial Thrombophlebitis

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**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 lower rates of VTEs and superficial thrombophlebitis extension and recurrence 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, 0.21 [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.

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**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

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of LMWH and Dose</th>
<th>Control</th>
<th>VTE, No. of Events/No. of Patients</th>
<th>LMWH Group</th>
<th>Control Group</th>
<th>RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steno, 2003</td>
<td>Enoxaparin, 40 mg sc once daily</td>
<td>Placebo</td>
<td>6/110</td>
<td>5/112</td>
<td>1.22 (0.38-3.89)</td>
<td></td>
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<tr>
<td></td>
<td>Enoxaparin, 1.5 mg/kg sc once daily</td>
<td></td>
<td>4/106</td>
<td>5/112</td>
<td>0.85 (0.23-3.06)</td>
<td></td>
</tr>
<tr>
<td>Cosmi, 2012</td>
<td>Parnaparin, 8500 IU sc once daily for 10 d</td>
<td>Parnaparin, 4250 IU sc once daily for 30 d</td>
<td>4/219</td>
<td>7/217</td>
<td>0.57 (0.17-1.91)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>followed by 6400 IU sc once daily for 20 d</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Parnaparin, 4250 IU sc once daily for 30 d</td>
<td>Parnaparin, 8500 IU sc once daily for 10 d</td>
<td>7/211</td>
<td>11/212</td>
<td>0.62 (0.25-1.57)</td>
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<tr>
<td></td>
<td>followed by 6400 IU sc once daily for 20 d</td>
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<tr>
<td>Vesalio, 2005</td>
<td>Therapeutic weight-adjusted nadroparin for 10 d followed by half dose for 20 d*</td>
<td>Nadroparin, 2850 IU sc once daily</td>
<td>2/81</td>
<td>4/83</td>
<td>0.51 (0.10-2.72)</td>
<td></td>
</tr>
<tr>
<td>Gorski, 2005†</td>
<td>Enoxaparin, 40 mg sc once daily</td>
<td>Heparin spray gel</td>
<td>1/23</td>
<td>3/21</td>
<td>0.30 (0.03-2.70)</td>
<td></td>
</tr>
<tr>
<td>Katzenschlager, 2003*</td>
<td>Enoxaparin, 40 mg sc once daily</td>
<td>Heparin spray gel</td>
<td>0/21</td>
<td>0/18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steno, 2003</td>
<td>Enoxaparin, 40 mg sc once daily</td>
<td>Tenoxicam, 20 mg once daily</td>
<td>6/110</td>
<td>4/99</td>
<td>1.35 (0.39-4.64)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enoxaparin, 1.5 mg/kg sc once daily</td>
<td>Tenoxicam, 20 mg once daily</td>
<td>4/106</td>
<td>4/99</td>
<td>0.93 (0.24-3.61)</td>
<td></td>
</tr>
<tr>
<td>Tilton, 1994</td>
<td>Nadroparin, 6150 IU sc once daily</td>
<td>Naproxen, 500 mg once daily</td>
<td>0/38</td>
<td>0/35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nadroparin, 61.5 IU/kg sc once daily</td>
<td>Naproxen, 500 mg once daily</td>
<td>0/36</td>
<td>0/35</td>
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<tr>
<td>Lozano, 2003</td>
<td>Enoxaparin, 1 mg/kg sc twice daily for the first wk, then 1 mg/kg for 3 wk</td>
<td>Saphenofemoral disconnection</td>
<td>0/30</td>
<td>2/30</td>
<td>0.20 (0.01-4.00)</td>
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<tr>
<td>Uncu, 2009</td>
<td>Ca-nadroparin, 190 IU/kg sc once daily</td>
<td>Ca-nadroparin, 190 IU/kg sc once daily + acetamin, 60 mg twice daily</td>
<td>0/25</td>
<td>0/25</td>
<td></td>
<td></td>
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<tr>
<td>Belcaro, 1999</td>
<td>Prophylactic LMWH + graduated compression stockings†</td>
<td>Graduated compression stockings</td>
<td>0/76</td>
<td>6/78</td>
<td>0.08 (0.00-1.38)</td>
<td></td>
</tr>
</tbody>
</table>

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).

* The RR could not be estimated.
† The outcome reported is deep vein thrombosis.

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. 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

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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, Daichi 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