# Cochrane for Clinicians

## *Putting Evidence into Practice*

## Anticoagulation for the Long-term Treatment of VTE in Patients with Cancer

**Michael J. Arnold, MD,** Uniformed Services University of the Health Sciences, Bethesda, Maryland

**Noah Cooperstein, MD,** Saint Louis University Southwest Illinois Family Medicine Residency Program, O'Fallon, Illinois

**Christopher Jonas, DO,** Uniformed Services University of the Health Sciences, Bethesda, Maryland

**Author disclosure:** No relevant financial affiliations.

### Clinical Question

What is the preferred anticoagulant for long-term prevention of recurring venous thromboembolism (VTE) in patients with cancer?

### Evidence-Based Answer

Low-molecular-weight heparin (LMWH), vitamin K antagonists, and direct oral anticoagulants, when used to prevent recurrent VTE, have a similar impact on all-cause mortality. Compared with vitamin K antagonists, LMWH reduces recurrent VTE in patients with cancer (number needed to treat = 19), with similar adverse event profiles.[1] (Strength of Recommendation: A, consistent, good-quality patient-oriented evidence.) Direct oral anticoagulants reduce VTE risk to the same extent as LMWH but at an increased risk of major bleeding (number needed to harm = 34).[1] (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

### Practice Pointers

Patients with cancer have an annual VTE risk of 1.3%, which is six times higher than patients without cancer.[2] The risk of VTE recurrence in patients with cancer can reach 29% at one year, leading to recommendations for long-term anticoagulation.[3] Cancer also conveys a high risk of major bleeding—up to 20% at one year for patients with both cancer and VTE.[4] This Cochrane review evaluated the safety and effectiveness of long-term anticoagulation to prevent VTE recurrence in patients with cancer.[1]

Sixteen randomized controlled trials involving 5,167 patients with cancer and diagnostically confirmed initial VTE were identified. Patients of all ages with solid or hematologic cancers at any stage were studied. The primary outcome was all-cause mortality; secondary outcomes included recurrent symptomatic VTE and major bleeding. The review evaluated large, multicenter trials and local studies with as few as 35 patients. Most multicenter trials were multinational, whereas the single-center trials were conducted in North America or Europe. Studies varied greatly in the medications used within each class. The larger studies were funded by the sponsoring pharmaceutical company.

Five studies that included 1,781 patients compared LMWH and vitamin K antagonists. There was no difference in mortality between groups. LMWH reduced recurrent symptomatic VTE compared with vitamin K antagonists (number needed to treat = 19; 95% CI, 14 to 34) in patients with cancer, with no difference in major bleeding between the two groups. One study reported no difference in thrombocytopenia between patients receiving LMWH and those receiving vitamin K antagonists.

Four studies with a total of 1,031 patients compared direct oral anticoagulants and vitamin K antagonists and found similar mortality rates, recurrent symptomatic VTE rates, and bleeding events between the groups. Data were low quality because of imprecise reporting and inclusion criteria.

Two studies compared LMWH and direct oral anticoagulants, but only one study, which included 1,016 patients, contained data sufficient for analysis. Mortality risk was similar between the groups, and there was no significant difference in recurrent symptomatic VTE between the direct oral anticoagulant and LMWH treatment

**These are** summaries of reviews from the Cochrane Library.

**This series** is coordinated by Corey D. Fogleman, MD, Assistant Medical Editor.

**A collection** of Cochrane for Clinicians published in *AFP* is available at https://www.aafp.org/afp/cochrane.

**CME This clinical content** conforms to AAFP criteria for continuing medical education (CME). See CME Quiz on page 673.

**SUMMARY TABLE: COMPARISON OF ANTICOAGULANTS TO PREVENT RECURRENT VTE AND MAJOR BLEEDING IN PATIENTS WITH CANCER**

| Intervention | Control | Outcomes | NNT/NNH | Number of participants (number of studies) | Quality of evidence |
|---|---|---|---|---|---|
| LMWH | Vitamin K antagonists | Recurrent VTE | NNT = 19 (95% CI, 14 to 34) Favored LMWH | 1,781 (5 RCTs) | Moderate |
| | | Major bleeding | No difference | | |
| Direct oral anticoagulants | Vitamin K antagonists | Recurrent VTE | No difference | 1,031 (4 RCTs) | Low |
| | | Major bleeding | No difference | | |
| Direct oral anticoagulants | LMWH | Recurrent VTE | No difference | 1,016 (1 RCT) | Low |
| | | Major bleeding | NNH = 34 (95% CI, 13 to 2,439) | | |

LMWH = low-molecular-weight heparin; NNH = number needed to harm; NNT = number needed to treat; RCT = randomized controlled trial; VTE = venous thromboembolism.

arms (relative risk = 0.69; 95% CI, 0.47 to 1.01). Patients using direct oral anticoagulants had an increased risk of major bleeding events compared with patients using LMWH (number needed to harm = 34; 95% CI, 13 to 2,439).

A recent systematic review concluded that direct oral anticoagulants do not significantly reduce VTE recurrence compared with LMWH, but they do increase major bleeding.[5] Guidelines from the American Society of Clinical Oncology, the American College of Chest Physicians, the European Society for Medical Oncology, and the National Institute for Health and Care Excellence recommend LMWH as first-line treatment for recurrent VTE in patients with cancer, which is consistent with the results of this Cochrane review.[1,6-8]

**The practice** recommendations in this activity are available at http://www.cochrane.org/CD006650.

**Editor's Note:** The numbers needed to treat and to harm, and the corresponding confidence intervals, were calculated by the authors based on raw data provided in the original Cochrane review.

**The views** expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of the Air Force, Uniformed Services University of the Health Sciences, Department of Defense, or the U.S. government.

## References


1. Kahale LA, Hakoum MB, Tsolakian IG, et al. Anticoagulation for the long-term treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev*. 2018;(6):CD006650.
2. Horsted F, West J, Grainge MJ. Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. *PLoS Med*. 2012;9(7):e1001275.
3. Chee CE, Ashrani AA, Marks RS, et al. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. *Blood*. 2014;123(25):3972-3978.
4. Kamphuisen PW, Beyer-Westendorf J. Bleeding complications during anticoagulant treatment in patients with cancer. *Thromb Res*. 2014;133 (suppl 2):S49-S55.
5. Li A, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): a systematic review and meta-analysis. *Thromb Res*. 2018;173:158-163.
6. Lyman GH, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31(17):2189-2204.
7. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in *Chest*. 2016;150(4):988]. *Chest*. 2016;149(2):315-352.
8. National Institute for Health and Care Excellence (NICE). Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. Clinical guideline [CG144]. Updated November 2015. https://www.nice.org.uk/Guidance/cg144. Accessed September 17, 2018.


# Alternative Interventions for Chronic Prostatitis/Chronic Pelvic Pain Syndrome in Men


**Anne L. Mounsey, MD, and Elizabeth Parks, MD,** University of North Carolina, Chapel Hill, North Carolina



**Author disclosure:** No relevant financial affiliations.


## Clinical Question

Are nonpharmacologic therapies safe and effective for men with long-standing pelvic pain and lower urinary tract symptoms, also known as chronic prostatitis/chronic pelvic pain syndrome?

## Evidence-Based Answer

In men with chronic pelvic pain and urinary dysfunction who have not responded to standard medical management, extracorporeal shock wave therapy reduces symptoms and increases quality of life. Acupuncture may also provide benefit to some patients.[1] (Strength of Recommendation: B, based on limited-quality patient-oriented evidence.)

Circumcision, transrectal thermotherapy, and physical activity demonstrated a statistically but not clinically

significant reduction in symptoms. It is unclear whether lifestyle modifications or prostatic massage provides any benefit. Most nonpharmacologic interventions are not associated with an increased risk of adverse events.[1] (Strength of Recommendation: B, based on limited-quality patient-oriented evidence.)

## Practice Pointers

Prostatitis is a common disorder affecting 10% to 14% of men in the United States, and it accounts for 1% of primary care visits each year.[2,3] Chronic prostatitis/chronic pelvic pain syndrome, defined as pelvic pain and lower urinary tract symptoms lasting more than three months, is a diagnosis of exclusion and comprises most cases. Men typically present with pain in the lower abdomen, perineum, testicles, or penis, as well as urinary symptoms and sexual dysfunction, including ejaculatory pain. The variety of presentations likely reflects the unclear etiology of this disease. As such, there is no standard first-line pharmacologic intervention. Antibiotics, nonsteroidal anti-inflammatory drugs, pregabalin (Lyrica), alpha blockers, and 5-alpha reductase inhibitors are most commonly used, and response to medical management is often limited.

This Cochrane review of 38 randomized controlled trials involving 3,290 men evaluated the effectiveness of several nonpharmacologic interventions for chronic prostatitis/chronic pelvic pain syndrome.[1] Participants were younger than 50 years. In 11 of 12 studies included in this meta-analysis, previous pharmacologic therapy had been unsuccessful. The primary outcome was the previously validated 13-question, 43-point National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI) scale, which assessed pain, urinary symptoms, and quality of life. On this scale, the minimal clinically important difference is considered a six-point reduction from baseline.

Extracorporeal shock wave therapy applied at the perineum demonstrated significant improvement in NIH-CPSI score vs. sham procedure at six weeks in three studies (mean difference [MD] = –6.18; 95% CI, –7.46 to –4.89), but this effect was no longer present at 12 and 24 weeks. Moderate evidence in one study supported improvement in sexual dysfunction with extracorporeal shock wave therapy vs. control.

Three high-quality studies (N = 204) found that acupuncture vs. a sham procedure likely improved symptoms at six to eight weeks (NIH-CPSI score MD = –5.79; 95% CI, –7.32 to –4.26). One study demonstrated persistent benefit at 24 weeks. However, there was no improvement in sexual dysfunction. In two lower-quality studies with inadequate blinding (N = 78), acupuncture provided statistical benefit (MD = –4.09; 95% CI, –6.87 to –1.30) compared with pharmacotherapy (i.e., levofloxacin [Levaquin], ibuprofen, or pollen extract).

Of the other interventions evaluated, few provided meaningful benefit. In one study of 700 men, circumcision provided statistical benefit on the NIH-CPSI score (MD = –3.00; 95% CI, –3.82 to –2.18) without a significant increase in adverse events at 12 weeks of follow-up. In one study of transrectal thermotherapy alone vs. medical therapy and another study of transrectal thermotherapy plus medical therapy vs. medical therapy alone, transrectal thermotherapy provided statistical, but not clinical, improvement (MD = –2.5; 95% CI, –3.8 to –1.2 and MD = –4.34; 95% CI, –5.65 to –3.04, respectively). Interestingly, in one low-quality study, physical activity reduced pain and increased quality of life, but worsened urinary symptoms. Prostatic massage, ultrasound, myofascial trigger point release, transurethral thermotherapy, transurethral needle ablation, and sono-electromagnetic therapy did not improve prostatitis symptoms. Evidence for the effectiveness of biofeedback, lifestyle modifications, laser therapy, tibial nerve stimulation, and transcutaneous electrical nerve stimulation was very low-quality because of the potentially high risk of bias.

Consensus guidelines suggest using individualized, symptom-based treatment for chronic prostatitis/chronic pelvic pain syndrome. Multimodal therapy is recommended because of the complex nature of this syndrome similar to other chronic pain disorders.[4] Evidence for nonpharmacologic interventions is generally limited, and many of the interventions are expensive and not widely available. Yet, given the desperate situation of many patients in whom standard medical management has failed, even small improvements in symptoms may be beneficial. Therefore, family physicians should consider extracorporeal shock wave therapy and acupuncture for the management of chronic prostatitis/chronic pelvic pain syndrome.

**The practice** recommendations in this activity are available at http://www.cochrane.org/CD012551.

## References


1. Franco JV, Turk T, Jung JH, et al. Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. *Cochrane Database Syst Rev.* 2018;(5):CD012551.
2. Bajpayee P, Kumar K, Sharma S, et al. Prostatitis: prevalence, health impact and quality improvement strategies. *Acta Poloniae Pharmaceutica.* 2012;69(4):571-579.
3. Collins MM, Stafford RS, O'Leary MP, et al. How common is prostatitis? A national survey of physician visits. *J Urol.* 1998;159(4):1224-1228.
4. Magistro G, Waenlaher FM, Grabe M, et al. Contemporary management of chronic prostatitis/chronic pelvic pain syndrome. *European Urol.* 2016;69(2):286-297. ■