



Q/ Does vaginal estrogen use increase the risk for adverse cardiovascular outcomes?

EVIDENCE-BASED ANSWER

A/ NO. In general, nonoral estrogen use for menopausal symptoms is associated with a lower cardiovascular (CV) risk profile than oral estrogen use (strength of recommendation [SOR], **B**; meta-analysis of cohort studies). Vaginal estrogen use is associated with lower risk for coronary heart disease (CHD) and similar risk for myocar-

dial infarction (MI), stroke, and deep vein thrombosis/pulmonary embolism (DVT/PE) compared with nonuse (SOR, **B**; cohort studies). Vaginal estrogen therapy also is associated with lower CV-related mortality for 3 to 5 years compared with nonuse (SOR, **B**; cohort study). No high-quality randomized trials address this topic.

Evidence summary

Cohort studies demonstrate no adverse CV outcomes

A 2020 systematic review and meta-analysis evaluated randomized controlled trials (RCTs) and observational studies to examine the association between menopausal hormone therapy and CV disease.¹ The 26 RCTs primarily evaluated oral hormone administration. The observational studies comprised 30 cohort studies, 13 case-control studies, and 5 nested case-control studies, primarily in Europe and North America; 21 reported the route of administration. The trials evaluated women ages 49 to 77 years (mean, 61 years), and follow-up ranged from 1 to 21.5 years (mean, 7 years). In subgroup analyses of the observational studies, nonoral hormone therapy was associated with a lower risk for stroke and MI compared to oral administration (see **TABLE 1**). Study limitations included enrollment of patients with few comorbidities, from limited geographic regions. Results in the meta-analysis were not stratified by the type of nonoral hormone therapy; only 4 studies evaluated vaginal estrogen use.

Two large cohort studies included in the

systematic review provided more specific data on vaginal estrogens. The first used data from the Women's Health Initiative in a subset of women ages 50 to 79 years ($n = 46,566$) who were not already on systemic hormone therapy and who did not have prior history of breast, endometrial, or ovarian cancer.² Data were collected from self-assessment questionnaires and medical record reviews. The median duration of vaginal estrogen use was 2 years, and median follow-up duration was 7.2 years. Vaginal estrogen users had a 48% lower risk for CHD (adjusted hazard ratio [aHR] = 0.52; 95% CI, 0.31-0.85) than nonusers. Rates for all-cause mortality (aHR = 0.78; 95% CI, 0.58-1.04), stroke (aHR = 0.78; 95% CI, 0.49-1.24), and DVT/PE (aHR = 0.68; 95% CI, 0.36-1.28) were similar. In this and the other cohort studies to be discussed, outcome data for all vaginal estrogen preparations (eg, cream, ring, tablet) were combined.

The other large cohort study in the systematic review evaluated data on postmenopausal women from the Nurses' Health Study.³ The authors evaluated health reports on 53,797 women as they transitioned through menopause. Patients with systemic

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TABLE

Associations between hormone therapy and cardiovascular disease^{1,a}

Cardiovascular outcome	Route	No. of cohort studies	Total no. of patients	Summary estimates ^b of risk ratios (95% CI)	I ² (%)	P value for heterogeneity
All-cause death	Oral	2	34,378	1.01 (0.94-1.08)	0.0	.75
	Nonoral	3	80,041	0.83 (0.65-1.07)	49.1	.14
Stroke	Oral	5	1,142,790	1.24 (1.11-1.39)	50.7	.09
	Nonoral	5	1,170,433	0.86 (0.77-0.96)	0.0	.91
Deep vein thrombosis/ pulmonary embolism	Oral	9	3,034,395	1.41 (1.19-1.67)	72.5	< .01
	Nonoral	7	2,117,900	0.81 (0.60-1.09)	70.8	< .01
Myocardial infarction	Oral	2	699,775	0.87 (0.57-1.32)	83.3	.01
	Nonoral	3	753,572	0.75 (0.60-0.93)	0.0	.45

^a Results vs no hormone therapy.

^b Weighted average of estimated intervention effects from individual studies.

hormone therapy use, history of cancer, and self-reported CV disease were excluded. After adjusting for covariates, the authors found no statistically significant difference between users and nonusers of vaginal estrogen and risk for total MI (aHR = 0.73; 95% CI, 0.47-1.13), stroke (aHR = 0.85; 95% CI, 0.56-1.29), or DVT/PE (aHR = 1.06; 95% CI, 0.58-1.93). Study limitations included low prevalence of vaginal estrogen use (< 3%), short duration of use (mean, 37.5 months), and lack of data on the type or dose of vaginal estrogen used. The study only included health professionals, which limits generalizability.

A Finnish cohort study (excluded from the systematic review because it used historical controls) compared rates of CHD and stroke in postmenopausal women who used vaginal estrogen against an age-matched background population. Researchers collected data from a nationwide prescription registry for women at least 50 years old who had purchased vaginal estrogens between 1994 and 2009 (n = 195,756).⁴ Women who purchased systemic hormone therapy at any point were excluded. After 3 to 5 years of exposure, use of vaginal estrogen was associated with a decreased risk for mortality from CHD (relative risk [RR] = 0.64; 95% CI, 0.57-0.70) and stroke (RR = 0.79; 95% CI, 0.69-0.91). However, after 10 years, these benefits were

not seen (CHD: RR = 0.95; 95% CI, 0.90-1.00; stroke: RR = 0.93; 95% CI, 0.85-1.01). All confidence interval data were presented graphically. Key weaknesses of this study included use of both vaginal and systemic estrogen in the comparator background population, and the failure to collect data for other CV risk variables such as weight, tobacco exposure, and blood pressure.

Recommendations from others

In 2022, the North American Menopause Society issued a Hormone Therapy Position Statement that acknowledged the lack of clinical trials directly comparing risk for adverse CV endpoints with different estrogen administration routes.⁵ They stated nonoral routes of administration might offer advantages by bypassing first-pass hepatic metabolism.

Similarly, the 2015 Endocrine Society Clinical Practice Guideline on the Treatment of Symptoms of the Menopause also stated that the effects of low-dose vaginal estrogen therapy on CV disease or DVT/PE risk had not been adequately studied.⁶

A 2013 opinion by the American College of Obstetricians and Gynecologists stated that topical estrogen vaginal creams, tablets, and rings had low levels of systemic absorption and were not associated with an increased risk for DVT/PE.⁷

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through bacterial, mycobacterial, or fungal cultures, and may be accompanied by elevated inflammatory markers or other systemic symptoms of the infection, setting it apart from pretibial myxedema.

Treatment is simple and noninvasive

Pretibial myxedema is usually asymptomatic, with minimal morbidity. The nodular variant may resolve spontaneously; thus, therapeutic management often is reserved for severe cases or for those with cosmetic concerns. Treatment options include mid- to high-potency topical corticosteroids with an occlusive dressing for 1 to 2 weeks (or until resolution) or an intralesional triamcinolone injection (5-10 mg/mL, single or monthly until resolution), compres-

sion stockings, and pneumatic compression.²

This patient was treated with a single intralesional injection of triamcinolone 10 mg/mL. The nodules resolved within a month. **JFP**

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CLINICAL INQUIRIES

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Editor's takeaway

The available evidence on vaginal estrogen replacement reassures us of its safety. After decades spent studying hormone replacement therapy with vacillating conclusions and opinions, these cohorts—the best evidence we may ever get—along with a consensus of expert opinions, consistently demonstrate no adverse CV outcomes. **JFP**

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