

# Blood Clot Risk Influenced by Hormone Therapy Administration Route in Women 50 and Older

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## Key Findings:

- Women aged 50 and older on hormone replacement therapy (HRT) administered on the skin are 22-27% less likely to experience various clotting disorders, such as stroke and embolism, compared to those treated with HRT administered vaginally.
- Women aged 50 and older on oral HRT are 26% more likely to have an arterial clot compared to those treated with vaginal HRT.

Hormone replacement therapy (HRT) is widely prescribed for postmenopausal women to alleviate symptoms and mitigate long-term health risks.<sup>1</sup> However, concerns about increased risk of blood clotting disorders have been raised, particularly regarding different routes of administration.<sup>2</sup> Prior studies suggest that oral estrogen might pose a greater risk for venous thromboembolism compared to transdermal estrogen, often applied as a patch or gel on the skin.<sup>2,3,4</sup>

To understand the real-world risk of blood clot disorders for women on HRT by route of administration, we studied 1,429,074 women aged 50 and older who initiated HRT between January 1, 2018, and March 1, 2023, and used only one HRT administration route during the study period. We studied injection, oral, transdermal, and vaginal administration routes. Patients who received their HRT vaginally were used as the baseline comparison group. We also factored in patient demographics, BMI, smoking status, and comorbid medical conditions, such as history of clots, hyperlipidemia, and cancer.

Women who were prescribed transdermal HRT were 22% less likely to have an ischemic stroke, 25% less likely to have a thromboembolism, 26% less likely to have a myocardial infarction (MI), and 27% less likely to have a pulmonary embolism (PE) compared to those who received their HRT vaginally. Women prescribed oral HRT were 26% more likely to have an arterial clot but 7% less likely to have a stroke compared to those who received their HRT vaginally. We did not observe a difference in the likelihood of clotting disorders between injectable HRT and HRT administered vaginally.

## Clot Disorder Likelihood by HRT Route

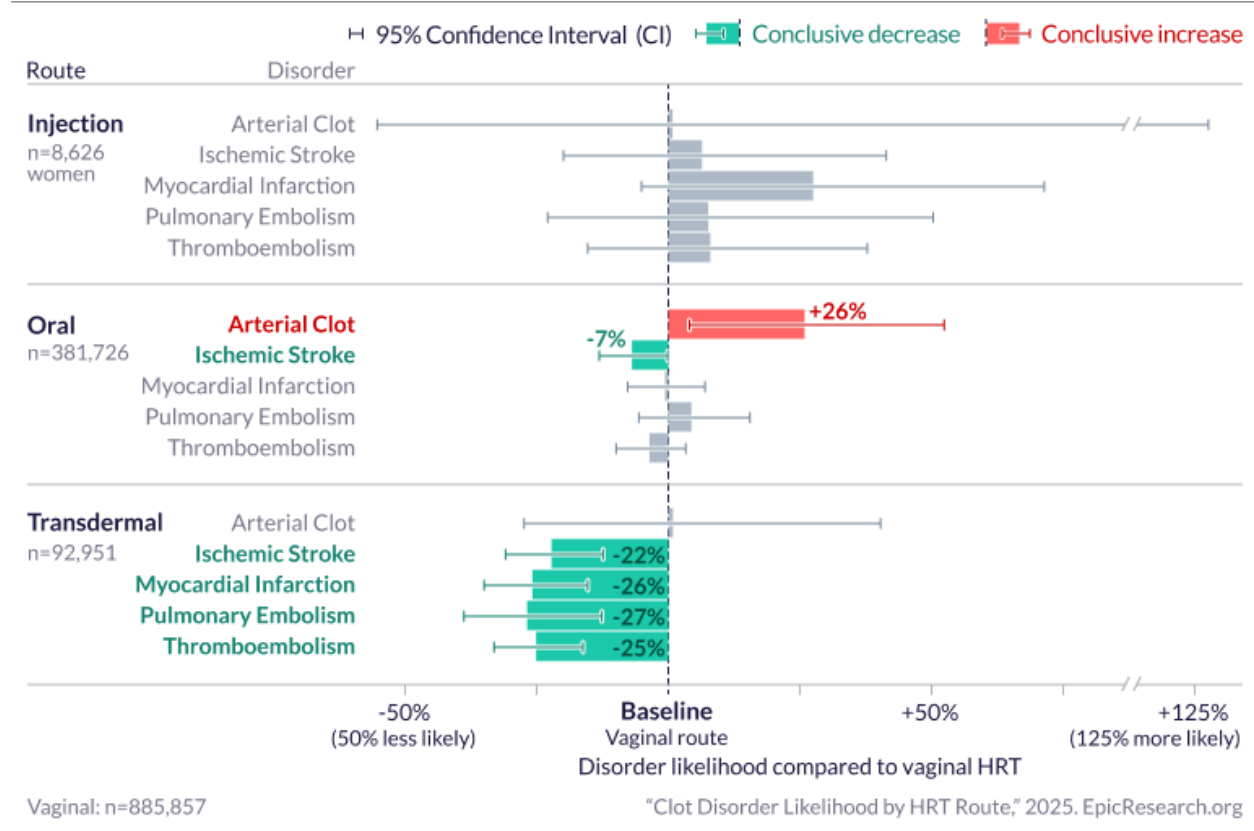


Figure 1. The likelihood of a woman experiencing a clot disorder by HRT route.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 298 million patient records from 1,700 hospitals and more than 39,000 clinics from all 50 states, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

## References

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3. Canonico M, Oger E, Plu-Bureau G, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840-845. doi:10.1161/CIRCULATIONAHA.106.642280
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## Data Definitions

Term	Definition
Study period	1/1/2018 to 3/1/2025
Study population: inclusion	Patients aged 50 and older with a legal sex of female with: <ul style="list-style-type: none"> <li>• Their first HRT ordered between 1/1/2018 and 3/1/2023</li> <li>• A face-to-face encounter at least two years after the exposure</li> </ul>
Study population: exclusion	Patients on both estrogen and progesterone during the two years after the exposure date
Exposures	Type of HRT (estrogen vs. progesterone) by route in the two years following initiation
Limitation	The dose and duration of the HRT were not included as factors.
Face-to-face encounter	An encounter with type Emergency, Office visit, Well Child, Follow-Up, Telemedicine, Urgent care, Walk-In, Inpatient Admission, HOV to Inpatient, or Emergency to Inpatient
Estrogen	A medication with RxNorm code 4083, 261472, 214549, 4099, 4103, 33747, 197679, 197680, or 4124, pharmaceutical class of "ESTROGENIC AGENTS" or "ESTROGEN/ANDROGEN COMBINATIONS," " pharmaceutical subclass of "Estrogens" or "Vaginal Estrogens," or simple generic name of "TESTOSTERONE ENAN/ESTRADIOL;" "ESTROGEN,ESTER/ME-TESTOSTERONE;" "ESTRADIOL/NORETHINDRONE ACET;" "ESTRADIOL/LEVONORGESTREL;" "ESTRADIOL/NORGESTIMATE;" "ESTRADIOL CYPIONATE;" "ESTRADIOL VALERATE;" "ESTRADIOL;" "ESTRONE;" "ESTROGENS, CONJUGATED;" "ESTROGENS,ESTERIFIED;" "ETHINYL ESTRADIOL;" "ESTROPIPATE;" "ESTROGENS,CONJ.,SYNTHETIC A;" "ESTRADIOL MICRONIZED;" "ESTRADIOL ACETATE;" "ESTROGENS,CONJ.,SYNTHETIC B;" or "DROSPIRENONE/ESTRADIOL"
Progesterone	A medication with RxNorm code 8727 or 7514, a pharmaceutical class of "PROGESTATIONAL AGENTS" or "ESTROGEN-PROGEST IN WITH ANTIMINERALOCORTICOID COMB," a pharmaceutical subclass of "Progestins," or simple generic name of "MEDROXYPROGESTERONE ACETATE," "HYDROXYPROGESTERONE CAPROATE," or "HYDROXYPROGESTERONE CAPROAT/PF"
Combination	A medication with RxNorm code 1251327, a pharmaceutical class of "ESTROGEN AND PROGESTIN COMBINATIONS" or "ESTROGEN-PROGESTIN WITH ANTIMINERALOCORTICOID COMB," or a pharmaceutical subclass of "ESTROGEN-PROGESTIN," or a simple generic name of "ESTROGEN,CON/M-PROGEST ACET"
Outcomes	Thromboembolism disorders: ICD-10-CM code I80*, I81*, or I82* Arterial clot: ICD-10-CM code I74* PE: ICD-10-CM code I26* Ischemic stroke: ICD-10-CM code I63* MI: ICD-10-CM code I21* or I22*
Confounders	Age: 50-64 or 65+ RUCA Social Vulnerability Index quintile BMI:

	<ul style="list-style-type: none"> <li>• Underweight: &lt;18.5</li> <li>• Healthy: 18.5 to &lt;25</li> <li>• Overweight: 25 to &lt;30</li> <li>• Obese: 30+</li> </ul> <p><b>Race and ethnicity</b></p> <p>Smoking history: Smoking status of Current or Former or packs per day or pack years value &gt; 0</p> <p>History of the following before the exposure:</p> <ul style="list-style-type: none"> <li>• Para and quadriplegia: ICD-10-CM code G81*, G82*, or G83*</li> <li>• Crohn's: ICD-10-CM code K50*</li> <li>• Ulcerative colitis: ICD-10-CM code K51*</li> <li>• CVD: ICD-10-CM code I20*-I26*, I30*-I39*, I40*-I49*, I51*, or I70*-I79*</li> <li>• Chronic lung disease: ICD-10-CM code J41*-J45*, J84*, E84*, J60, J67.8, J69.8, or J82.83</li> <li>• Hyperlipidemia: ICD-10-CM code E78.2*-E78.5*</li> <li>• Prior blood clots: ICD-10-CM code I80*, I81*, I82*, I74*, or I26*</li> <li>• Stroke: ICD-10-CM code I60*, I63*, I69.3*, Z86.73 or G45.9</li> <li>• MI: F01*, F02*, or F03*</li> <li>• Cancer: ICD-10-CM code C*</li> </ul>
<b>Route</b>	<p>Oral: "oral"</p> <p>Vaginal: "vaginal"</p> <p>Transdermal: "transdermal" or "topical"</p> <p>Injection: "intramuscular," "injection," "subcutaneous," or "intravenous"</p>
<b>Race and ethnicity</b>	Non-exclusive flags for Black and Hispanic patients
<b>Model specifications</b>	Logistic Regression
<b>RUCA</b>	Rural-Urban Commuting Area is a classification of geographic areas based on population density, urbanization, and daily commuting. It ranges from 1 to 10, with lower values indicating more urban areas and higher values indicating more rural areas.
<b>Social Vulnerability Index</b>	The social vulnerability quintile for the ZIP Code of the patient's most recent address.

**Table 1: Clot Disorder Likelihood by HRT Route**

Route	Outcome	Odds Ratio	0.025	0.975
Injection	Arterial Clot	1.008	0.447	2.276
Injection	Ischemic Stroke	1.064	0.801	1.414
Injection	Myocardial Infarction	1.275	0.949	1.714
Injection	Pulmonary Embolism	1.076	0.771	1.503
Injection	Thromboembolism	1.080	0.847	1.378
Oral	Arterial Clot	1.259	1.040	1.524
Oral	Ischemic Stroke	0.931	0.869	0.999
Oral	Myocardial Infarction	0.994	0.923	1.070
Oral	Pulmonary Embolism	1.044	0.944	1.155

Oral	Thromboembolism	0.964	0.901	1.033
Topical	Arterial Clot	1.009	0.726	1.403
Topical	Ischemic Stroke	0.778	0.691	0.876
Topical	Myocardial Infarction	0.742	0.650	0.847
Topical	Pulmonary Embolism	0.732	0.612	0.874
Topical	Thromboembolism	0.749	0.669	0.838