

Hormone Therapy Timing and Heart Risk

Executive Summary for practitioners

REPORT	Hormone replacement therapy and cardiovascular risk in postmenopausal women
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DESIGN	Review of major randomized trials, national registries and meta-analyses

OVERVIEW

This 2026 review synthesizes the cardiovascular evidence on hormone therapy across landmark randomized trials, large national registry data and recent meta-analyses. Its organizing argument is that cardiovascular outcomes depend less on whether hormone therapy is used than on four modifying variables: timing of initiation relative to menopause, hormone formulation, route of administration, and baseline cardiovascular risk. The review sets this against a clinical backdrop in which cardiovascular disease is the leading cause of death among women, exceeding deaths from all cancers combined.

KEY FINDINGS

- Initiation **within 10 years of menopause or before age 60** is consistently associated with cardiovascular benefit; later initiation is associated with increased stroke and venous thromboembolism risk.
- In a Swedish register study of 919,614 women including 77,512 hormone therapy initiators, **transdermal estrogen showed no significant increase** in cardiovascular risk, while oral continuous combined therapy showed a modest increase in ischemic heart disease.
- A 2024 meta-analysis of 33 randomized trials and 44,639 women found **no reduction in all-cause mortality or major cardiovascular events overall**, with increased stroke and venous thromboembolism risk, but better outcomes among early initiators.
- Oral estrogens undergo hepatic first-pass metabolism, stimulating coagulation factor production; transdermal delivery bypasses this and shows neutral or favorable effects on blood pressure and clot risk.
- Trial results long treated as contradictory align once timing is accounted for: DOPS and ELITE enrolled recently postmenopausal women and found benefit; WHI enrolled women aged 50–79 on one oral formulation and found harm.
- Widely used cardiovascular risk calculators do not incorporate menopause-specific variables and may underestimate risk in younger postmenopausal women.

CLINICAL IMPLICATIONS

The practical takeaway is that the hormone therapy cardiovascular conversation has four variables, not one. A patient at low cardiovascular risk within a decade of menopause sits in a materially different position from a patient with established disease starting fifteen years out, even on the same prescription. Guidance from NICE,

the British Menopause Society and the North American Menopause Society has converged on individualized assessment and shared decision-making, with transdermal delivery generally favored where thrombotic risk is elevated.

| PATIENT IMPACT

Public understanding of hormone therapy and the heart is still substantially shaped by early 2000s reporting of trials that tested one oral formulation in a population older than the typical candidate. Many symptomatic women avoid discussing hormone therapy at all as a result. This review supports reopening that conversation on more accurate terms — not as blanket reassurance, but as a risk assessment specific to the individual's timing, formulation, route and baseline cardiovascular health.

| IMPLEMENTATION CONSIDERATIONS

- **Clinical:** Document time since menopause explicitly; it is a primary variable in the risk assessment, not background information.
- **Clinical:** Favor transdermal delivery where thrombotic risk factors are present, including prior clot, obesity, or smoking.
- **Clinical:** Assess baseline cardiovascular status before initiating, recognizing that standard calculators may underestimate risk in this group.
- **Communication:** Proactively address early-2000s trial coverage rather than waiting for patients to raise it.

| LIMITATIONS & CONTEXT

This is a narrative review rather than a systematic review or meta-analysis, so study selection and weighting reflect editorial judgment. Much of the underlying evidence comes from populations that underrepresent racial and ethnic minority groups, including the Women's Health Initiative. Long-term cardiovascular safety data for newer formulations remains limited, as does high-quality comparative evidence between progestogen types. Data on women with premature ovarian insufficiency or early menopause, who often need longer treatment duration, is described as scarce. The review also draws on UK epidemiology and guidance, which may not map exactly onto other systems.

| RECOMMENDED NEXT STEPS

1. Review patients currently on oral hormone therapy who carry thrombotic risk factors for possible transition to transdermal.
2. Add time since menopause as a standard documented field for patients on or considering hormone therapy.
3. Prepare a short response to the Women's Health Initiative question, which remains the most common patient objection.
4. Reassess hormone therapy decisions periodically rather than treating the initial decision as permanent.

RESEARCH SOURCE CITATION

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