

# Hormone replacement therapy is hot again!

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**Article summary:** Hormone replacement therapy (HRT) for menopausal hot flashes at the time of menopause leads to more benefit than risk.

## Hormone replacement therapy: a brief history

Prior to 2002 it was known that hormone therapy alleviated vasomotor symptoms of menopause and provided bone health benefits. Observational data implied that cardiovascular health was improved, but this was not studied in a trial until the Women's Health Initiative (WHI) study, which tested the risks and benefits of oral conjugated estrogen (CEE) 0.625mg/day +/- medroxyprogesterone acetate (MPA, a synthetic progestin) 2.5mg/day.<sup>1</sup> Surprisingly, the primary endpoint of coronary heart disease (CHD, defined as non-fatal myocardial infarction and CHD death) was actually increased, though not statistically significant. There also appeared to be an increased risk of stroke, which was a secondary outcome. A media frenzy ensued, and prescriptions for estrogen/progesterone dropped dramatically.<sup>2</sup> Lost in the hysteria that followed was the fact that only 3.5% of the women were aged 50-54, and the average age of the women in the study was 63. Additionally, only a fraction of the women had vasomotor symptoms at trial initiation.<sup>2</sup> In recent years, the WHI has been re-examined, and physicians are keener to use



hormones in specific situations. Here, we will review the use of hormones specifically for treating hot flashes.

## Menopause and Estrogen

Two types of estrogen are produced by the adult, non-pregnant human female. Estradiol (E2) is the most potent, produced by the ovarian follicle. Estrone (E1) is a less potent estrogen made primarily in the adrenal glands and other tissues like fat. During menopause, estradiol levels drop by 90%, estrone levels drop by 30%. Consequently, estrone is the dominant estrogen post menopause.

## What do we mean by hormone replacement?

Usually this means estrogen, though progesterone is also given to women with an intact uterus. The most common estrogens used for menopausal symptoms include conjugated equine estrogens, micronized estradiol, and transdermal estradiol (Figure 1). Oral doses are generally much lower than that tested in the WHI trial. Transdermal

estradiol is often considered first line, as there may be less risk of stroke and venous thromboembolism (not confirmed in randomized controlled trials).<sup>3</sup> Transdermal preparations bypass metabolism in the liver and eliminate absorption issues that may arise with oral preparation. The progestogen most used today is micronized progesterone.

### Key considerations from the WHI

- Breast cancer was the primary safety outcome, and there was a statistically significant increase in breast cancer cases in the CEE/MPA group. The increase was about one extra case per 1000 women treated. Incidence remained elevated at 20 years (but not mortality).<sup>4</sup> Importantly, there was a decrease in breast cancer cases in the CEE alone group, though this did not reach statistical significance.
- In women taking both CEE and MPA, the primary endpoint of CHD was lower in women aged 50-59 than older groups. At follow-up of 13 years, any CHD risks were back to baseline, and there was no statistically significant difference in all-cause mortality in any age group.<sup>5</sup> Additionally, women aged 50-59 on CEE alone had lower cardiovascular events than women taking placebo.
- A reanalysis of the original data found no difference in stroke risk in women aged 50-59 years of age.<sup>6</sup>
- At baseline the CEE/MPA group included 48% with high blood pressure, and 48% were former smokers (10% current smokers). In the CEE alone group, 36% had high

blood pressure, 40% were former smokers (11% current smokers).

### Society guidelines

The menopause society recommends hormone replacement therapy for symptomatic women less than 60 years old or within 10 years of menopause who lack contraindications (breast cancer, active thromboembolic disease, uncontrolled cardiovascular disease).<sup>3</sup>

### Acknowledgements

Many thanks to Dr. Sandra Rice, MD, who inspired me to write this article. Her 2019 book titled “The Estrogen Question. Know Before You Say No to HRT” is an excellent overview of all aspects of hormone replacement therapy.

### References

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## Suggested Reading

For an in-depth review of the WHI see JAMA. 2024;331(20):1748-1760.

For an in-depth review of the long-term risks and benefits of hormone replacement therapy see IntJ.Mol.Sci.2025;26:11098

Figure 1

