

## Effect of Hormone Replacement on Cognitive Function in Postmenopausal Women

Grady D, Yaffe K, Kristof M, et al. Effect of postmenopausal hormone therapy on cognitive function: the Heart and Estrogen/progestin Replacement Study. *Am J Med* 2002;113:543–8.

### Study Overview

**Objective.** To determine if hormone replacement therapy (HRT) results in better cognitive function in postmenopausal women.

**Design.** Randomized, placebo-controlled, double-blinded trial with an intention-to-treat analysis.

**Setting and participants.** Study participants were selected from a larger 20-site, multicenter trial. 10 centers were selected for the ancillary study. Participants were postmenopausal women younger than 80 years old, previously diagnosed with coronary artery disease, and with an intact uterus.

**Intervention.** Patients were randomly assigned to receive either placebo or daily oral conjugated estrogen (0.625 mg) and medroxyprogesterone acetate (2.5 mg) in one tablet. The mean duration of study treatment was  $4.2 \pm 0.4$  years.

**Main outcome measures.** At the final visit of the trial, patients completed a battery of 6 validated cognitive function tests: the modified Mini-Mental Status Examination, Verbal Fluency, modified Boston Naming, Word List Memory, Word List Recall, and Trials B. The primary outcome was the scores on these tests. Cognitive function tests were not performed at baseline.

**Main results.** 1328 women were enrolled in the study, with 662 randomly assigned to the intervention and 666 to placebo. 517 (78%) patients in the study group and 546 (82%) patients in the control group participated in the cognitive testing. Reasons for not completing the study included death, inability to complete the cognitive testing, refusal to give informed consent, and loss to follow-up. The intervention and the placebo groups were similar with regard to almost all baseline and follow-up measures except age and years since menopause (the intervention group was approximately 1 year younger and had approximately 1 less year since menopause). By the end of the trial, 78% (401/517) of women assigned to the intervention and 84% (460/546) of those assigned to placebo reported taking at least 80% of the

study medications. There were no statistically significant differences in age-adjusted cognitive function scores between the 2 groups on 5 out of 6 measures. In the Verbal Fluency test, the intervention group performed slightly worse than women assigned placebo ( $15.9 \pm 4.8$  versus  $16.6 \pm 4.8$ ;  $P = 0.02$ ). Results remained unchanged after 2 subgroup analyses (ie, women who were older than 70 years at the start of the trial and patients who were greater than 80% compliant with the study medication).

**Conclusion.** HRT did not result in better cognitive function for postmenopausal women with coronary artery disease.

### Commentary

With the aging of the population and the expected increase in Alzheimer's prevalence, any therapy that might offer potential cognitive protective effects must be carefully evaluated. Some studies have suggested that HRT might slow cognitive decline and progression to dementia, but the evidence has been conflicting. The lack of a definitive answer comes partly from weaknesses in prior study designs. Earlier studies have utilized smaller numbers of patients and have not compared the outcomes in patients receiving therapy with controls. Grady et al's study has addressed these earlier concerns by enrolling larger numbers of patients and comparing women receiving HRT with women receiving placebo.

Despite these strengths, this study still has several weaknesses that make it difficult to generalize the results. First, no baseline measurement of cognitive impairment was obtained. However, the trial was sufficiently large enough that the randomization process should have equally distributed patients entering the study with preclinical dementia.

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Second, the mean duration of the study was only 4 years. It is unclear if this is enough time for a potential protective effect of estrogen to be evident, particularly in light of the fact that the patients' mean age was 71 years. Third, the therapy used in the trial was an estrogen/progestin combination, and prior studies that have seen a beneficial effect have used estrogen alone. Perhaps the addition of progesterone mitigates estrogen's protective effect.

### **Applications for Clinical Practice**

Postmenopausal hormone replacement with an estrogen/progestin combination does not appear to improve cognitive function in women with coronary disease. It remains unclear whether initiating HRT prior to symptomatic onset or longer durations of therapy might result in better cognitive outcomes.

*—Review by Harvey J. Murff, MD, MPH*

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