

Short-term Use of Low-Dose Estrogen and Cardiac Events

Grodstein F, Manson JE, Colditz GA, et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000;133:933-41.

Study Overview

Objective. To assess the relative risk of coronary events and stroke among women taking varying doses of estrogen, with or without progestin, for primary prevention of cardiovascular disease.

Design. Prospective, observational cohort study.

Setting and participants. Subjects were identified from the Nurses' Health Study, which was begun in 1976 with a cohort of 121,700 female nurses aged 30 to 55 years. Women who reported stroke, myocardial infarction (MI), angina pectoris, coronary revascularization, or cancer (except nonmelanoma skin cancer) were excluded. All other subjects were analyzed from the time that they became postmenopausal (21,947 initially and 48,586 during subsequent biennial follow-ups, with a total of 808,825 person-years available for analysis). Participants were excluded from subsequent analyses after their first cardiovascular event.

Main exposures. Hormone use as determined by self-report on a mailed questionnaire. Participants provided information on types and doses of hormones being taken. For study analyses, onset of hormone therapy was assumed to be at the start of the first biennial assessment for which participants reported use; therapy was assumed to continue up to the biennial assessment for which participants reported no use.

Potential confounders. Analyses were adjusted for the following variables, all of which were updated biennially: age (categorized in 5-year groups), body mass index (6 groups), cigarette smoking (never; past; or current smoker, stratified into 4 categories of use), self-reported history of hypertension (yes or no), diabetes (yes or no), and elevated cholesterol level (yes or no). Other data used in multivariate adjustments were collected only once: type of menopause (natural or surgical), age at menopause (3 age-groups), parental MI before age 60 years (yes or no), and previous oral contraceptive use (yes or no). For some analyses, additional variables were included: saturated fat intake (quintiles), alcohol use (none or 3 levels of use), vitamin E supplementation (yes or no), multivitamin use (yes

or no), aspirin use (none, 1 to 6 per week, or more than 7 per week), and physical activity (none or at least once per week). Information on these variables was updated every 4 years.

Main outcome measures. Primary endpoints were fatal and nonfatal MI and stroke and sudden cardiac death.

Main results. Overall, current use of hormone therapy was associated with an age-adjusted relative risk (RR) for coronary events of 0.54 (95% confidence interval [CI], 0.46 to 0.62). Adjustments for potential confounders modestly attenuated this risk (0.61 to 0.64, depending on the variable). Risk reduction decreased with longer use (RR from 0.30 [95% CI, 0.16 to 0.58] for up to 1 year to 0.69 [0.56 to 0.85] at 10 years or more; *P* for trend not reported). Hormone use did not significantly affect overall risk for stroke (RR, 1.13 [95% CI, 0.94 to 1.35] for current users and 1.32 [95% CI, 0.76 to 2.32] for short-term users compared with never-users). For combined cardiovascular events (coronary heart disease plus stroke), a lower rate of cardiovascular disease was found among current hormone users compared with never-users (RR, 0.77 [95% CI, 0.69 to 0.87]).

Analyses of different estrogen doses revealed similar risk reductions for coronary events (RR for users taking 0.625 mg/day, 0.54 [95% CI, 0.44 to 0.67] versus RR for those taking 0.3 mg/day, 0.58 [95% CI, 0.37 to 0.92]). However, RR for stroke was substantially different among women taking different estrogen doses. Subjects using 0.3 mg/day showed a nonsignificant decreased risk (RR, 0.54 [95% CI, 0.28 to 1.06]), while users of higher doses had significantly increased risks directly related to dose (RR for 0.625 mg/day, 1.35 [95% CI, 1.08 to 1.68]; RR for 1.25 mg/day or more, 1.63 [1.18 to 2.26]). Women taking estrogen alone and those taking estrogen plus progestin had a similarly reduced risk of coronary events (RR, 0.55 [95% CI, 0.45 to 0.68] versus 0.64 [95% CI, 0.49 to 0.85], respectively); however, estrogen-plus-progestin users had a 45% higher risk for stroke than subjects who had never used hormone therapy (RR, 1.45 [95% CI, 1.10 to 1.92]). These results did not change significantly when adjusted for estrogen dose.

Conclusion

The Nurses' Health Study continues to support the hypothesis

that hormone replacement therapy can reduce the incidence of major coronary events. Lower doses and use of estrogen alone seem to confer equal or greater benefits and to eliminate possible increased risk of stroke.

Commentary

The Nurses Health Study is one of the largest prospective cohorts ever assembled. Its methodologies, in terms of design and analysis, are excellent. Nonetheless, it is still an observational study. Editorialists [1] who have commented on Grodstein and colleagues' article point out 2 principle reasons why these findings should be examined with a skeptical eye. First, 2 moderately large studies examining hormone use for *secondary* prophylaxis—as opposed to *primary* prophylaxis in the present article—showed a risk increase during the first 1 to 2 years of use [2,3]. Moreover, the Women's Health Initiative, an ongoing large randomized controlled trial testing primary prophylaxis, recently released early findings that appear to point to an association between increased risk of stroke and hormone replacement [4]. Second, the editorialists discussed information suggesting that adherence with any prophylactic drug treatment (or its placebo) seems to be associated with improved outcomes and cannot be explained by typically measured variables. A third reason to be skeptical about the validity of Grodstein and colleagues' results appears in their own article: a clear trend that suggests a substantially decreased benefit with longer hormone use.

Applications for Clinical Practice

Until supportive results from other randomized controlled trials are available, hormone replacement therapy is not recommended for cardiovascular disease prevention. Women who wish to take hormones for menopausal symptoms or osteoporosis should start with lower doses (eg, 0.3 mg/day) and use unopposed estrogen when possible. Providers should carefully review potential risks and benefits of hormone replacement therapy for women who want to begin or continue a course of hormones for cardiovascular prophylaxis.

References

1. Grady D, Hulley SB. Hormones to prevent coronary disease in women: when are observational studies adequate evidence? *Ann Intern Med* 2000;133:999–1001.
2. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998; 280:605–13.
3. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. *N Engl J Med* 2000;343:522–9.
4. Lenfant C. Statement from Claude Lenfant, MD, Director, National Heart, Lung, and Blood Institute, on preliminary trends in the Women's Health Initiative [press release]. Washington (DC): National Heart, Lung, and Blood Institute Communications Office; 3 April 2000.

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