Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.

Review: Observational studies adjusting for socioeconomic status and lifestyle show no association between HRT and CAD

Humphrey LL, Chan BK, Sox HC. **Postmenopausal hormone replacement therapy and the primary prevention of cardiovascular disease.** Ann Intern Med. 2002;137:273-84.

QUESTION

What is the effectiveness of postmenopausal hormone replacement therapy (HRT) for primary prevention of cardiovascular disease?

DATA SOURCES

Studies were identified by searching MEDLINE and Cochrane databases from 1966 to December 2000 and by reviewing bibliographies of relevant studies and other publications.

STUDY SELECTION

Studies were selected if they were randomized controlled trials (RCTs), cohort studies, or case–control studies that assessed the use of HRT for primary prevention of cardiovascular disease in postmenopausal women and if English-language abstracts were available.

DATA EXTRACTION

Data were extracted on study design, type of HRT (unopposed estrogen or estrogen plus progestin), definitions of cardiovascular disease, and potential risk factors included in multivariate models. 2 investigators independently assessed the quality of individual studies. Formal review and meta-analysis were limited to studies of good or fair quality and included RCTs, cohort studies with internal controls, and population-based case–control studies with ≥ 3 years of follow-up. HRT use was classified as current, past, ever, or any (combined current, past, or ever).

MAIN RESULTS

Only the results for coronary artery disease (CAD) incidence are reviewed here (3 cohort studies, 9 case–control studies, and 1 small RCT). Studies that did not adjust for socioeconomic status (SES) found that current and past use of HRT reduced CAD incidence, whereas studies that adjusted for SES found no association between any measure of HRT use and CAD (Table). Similar results were found when analyses were stratified by studies that adjusted for alcohol consumption, exercise, or both.

CONCLUSIONS

Meta-analysis of studies that adjust for socioeconomic status or alcohol consumption and exercise shows that current, past, ever, or any use of HRT does not reduce coronary artery disease (CAD). Studies that do not adjust for these factors show a reduced risk for CAD with current and past use.

Source of funding: Agency for Healthcare Research and Quality.

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Relative risk for coronary artery disease according to use of hormone replacement therapy (HRT)

Use of HRT	Relative risk (95% credible interval)	
	Unadjusted*	Adjusted†
Current	0.71 (0.64 to 0.78)	0.97 (0.82 to 1.16)
Past	0.78 (0.69 to 0.87)	1.07 (0.90 to 1.27)
Ever	Not reported	1.11 (0.84 to 1.53)
Any	Not reported	1.04 (0.79 to 1.44)

*Includes data from studies that did not adjust for socioeconomic status.
†Includes data from studies that adjusted for socioeconomic status.

COMMENTARY

The 2 meta-analyses by Humphrey and colleagues and Nelson and colleagues, and much of the medical literature, do not clearly define postmenopausal HRT. Although authors often claim that many observational studies show the benefits of HRT on CAD risk, the data almost completely relate to unopposed estrogen (1). Few epidemiologic studies have evaluated estrogen plus progestin administered as continuous combined therapy. A limited number of studies were included in the meta-analyses by Humphrey and Nelson and their colleagues, and the included studies sometimes failed to specify type of HRT. Studies published in the 1980s and earlier likely refer to unopposed estrogen therapy.

The lack of specificity in type of HRT is problematic because of the potential for different effects of estrogen alone and estrogen plus progestin. It is important to note that the meta-analyses used a common protocol to apply standard criteria for quality (2) and included only studies of higher quality. For studies assessing CAD outcomes, the authors identified a relation between poorer quality studies and greater protection against CAD.

Changing patterns of use (estrogen alone replaced by combined estrogen plus progestin) and indications for use (e.g., starting women on therapy before menopause to reduce bone loss) may account, in part, for differences in results. Also, acute effects of combined therapy (e.g., the prothrombotic and proinflammatory effects of progestins) may be missed in prospective studies because of lack of attention to early events and follow-up.

Data from both epidemiologic studies and RCTs of HRT consistently show other thrombotic effects, such as stroke and pulmonary embolus. This argues, at least in part, against a bias related to this pathway in the observational studies. Although SES appears as one other important variable in this analysis, the authors note that the range of cardiovascular risk factors controlled for in observational studies also varied substantially. The authors, however, did not point out that studies that controlled for SES observed similar results before and after such control, which suggests that this is not an explanation for the discrepancy between RCT and observational study results. Is confounding by indication changing over time concurrent with changing patterns of drug combination? Is SES merely a marker for more recent studies that evaluate estrogen plus progestin? Alternatively, is the timing of exposure in relation to menopause the explanatory factor? Animal studies suggest

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Review: Risks and benefits of HRT comparing various sources of evidence

Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. **Postmenopausal hormone replacement therapy: scientific review.** JAMA. 2002;288:872-81.

QUESTION

What are the benefits and harms of hormone replacement therapy (HRT) for primary prevention of cardiovascular disease, thromboembolism, osteoporosis, cancer, dementia, and cholecystitis?

DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 2001), HealthSTAR (1975 to 2001), and the Cochrane Controlled Trials Register; reviewing bibliographies of relevant studies, reviews, and editorials; and contacting experts.

STUDY SELECTION

Studies were selected if they included a comparison group of HRT nonusers and reported data relating to HRT use and clinical outcomes of interest. Studies were excluded if the sample was selected according to previous events or conditions associated with higher risks for targeted outcomes.

DATA EXTRACTION

Data were extracted on study design and type of HRT (unopposed estrogen or estrogen plus progestin). 2 reviewers independently assessed study quality as good, fair, or poor using the U.S. Preventive Services Task Force (USPSTF) criteria.

MAIN RESULTS

The findings of the meta-analyses (relative risks) for some outcome categories are summarized in the Table with corresponding hazard ratios from the recent Women's Health Initiative (WHI). The results of the meta-analysis showed that HRT reduced the risk for wrist fractures, vertebral fractures, colon cancer, and dementia, and increased the risk for stroke, thromboembolic events, breast cancer, and cholecystitis (Table). Findings for some of these outcomes were available from the WHI randomized controlled trial and differed (in terms of statistical significance when using adjusted results for secondary outcomes) for vertebral fractures, colon cancer, coronary heart disease events, and stroke (Table).

CONCLUSIONS

Results of this meta-analysis of primarily observational studies and those of a large randomized controlled trial (Women's Health Initiative [WHI]) both show that hormone replacement therapy (HRT) increases risk for thromboembolic events. The meta-analysis shows no effect of HRT on coronary heart disease events, whereas the WHI found an increased risk.

Sources of funding: Agency for Healthcare Research and Quality and Portland Veterans Affairs Medical Center Women's Health Fellowship.

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Risks associated with ever use of HRT from Nelson and colleagues and from the Women's Health Initiative [WHI])*

Outcomes	Relative risk (95% CI) from Nelson and colleagues	Hazard ratio (CI) from WHI
Hip fractures	0.76 (0.56 to 1.01)	0.66 (0.33 to 1.33)‡
Vertebral fractures	0.60 (0.36 to 0.99)†	0.66 (0.32 to 1.34)‡
Colon cancer	0.80 (0.74 to 0.86)†	0.63 (0.32 to 1.24)‡
Coronary heart disease events	0.91 (0.67 to 1.33)	1.29 (1.02 to 1.63)†
Stroke	1.12 (1.01 to 1.23)†	1.41 (0.86 to 2.31)‡
Thromboembolic events (current use)	2.14 (1.64 to 2.81)†	2.11 (1.26 to 3.55)†‡
Breast cancer (≥ 5 y HRT)	1.23 to 1.35	1.26 (1.00 to 1.59)†

*Abbreviations defined in Glossary; meta-analyses based on a random-effects model.
†Statistically significant.
‡Adjusted CIs.

COMMENTARY *(continued from page 40)*

that estrogens have beneficial effects in the early stages of atherogenesis but reduced beneficial effects in the final stages of plaque complications (3).

How can drug formulation change over time and most associations observed in epidemiologic studies (i.e., breast cancer, pulmonary embolus, stroke, colon cancer, cholecystitis, and osteoporotic fracture) be consistent, and yet CAD outcomes diverge? Consistent evidence across the RCTs argues against chance.

The consistency between non-RCTs and RCTs for noncardiac outcomes is reassuring and supports other evaluations of the contribution of different study designs to evaluation of medical therapies (4–7). Such studies comparing designs may be limited in power, but on average, well-designed observational studies show a similar magnitude of estimated benefits as RCTs. We should not focus solely on study design but must also consider the formulation and timing of use of postmenopausal HRT that is being evaluated.

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