

SOUNDING BOARD

Understanding the Divergent Data on Postmenopausal Hormone Therapy

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Recent findings from clinical trials examining the relation between postmenopausal hormone therapy and coronary heart disease^{1,2} have appeared to be widely divergent from the results of earlier observational studies. In randomized clinical trials, subjects are randomly assigned to treatments, thereby minimizing possible differences between the groups in lifestyle or health-related factors. In observational studies, by contrast, subjects who choose to take a given agent may be very different from those who do not. Although apparent discrepancies in results have raised questions about the validity of observational data, it is useful to explore both the methodologic and the biologic issues that may have contributed to the differences (Table 1). Elucidation of these factors will improve our understanding of the data and, more important, inform future research in this complex and challenging area.

It is important to bear in mind that numerous health practices other than hormone therapy have been examined in observational epidemiologic studies and in trials. For some of these other practices (such as the use of antioxidant vitamins for the prevention of cardiovascular disease^{3,4}), possible inconsistencies have also been seen between the two types of studies; but in many instances, findings have been consistent,⁵ including those with respect to practices (such as fish oil consumption^{6,7}) that are probably subject to confounding similar to that found with hormone use. Indeed, apart from studies focused on coronary heart disease, results of clinical trials have been remarkably similar to observational data with regard to the relation between hormone therapy and all other conditions that have been examined (stroke, venous thromboembolism, breast cancer, colon cancer, and hip fracture) (Table 2).

With respect to breast cancer, for example, the similarities between data from observational studies and those from clinical trials are impressive, and are also concordant with experimental data from nonhuman primates.¹³ The Women's Health Ini-

tiative trial (WHI)¹ found a relative risk of invasive breast cancer associated with combined hormone therapy of 1.26 (mean follow-up, 5.2 years) and a trend toward increasing risk with increasing duration of therapy. In an overview of 51 observational studies,¹⁴ less than five years of therapy with estrogen combined with progestin was associated with a 15 percent increase in the risk of breast cancer, and the increase was greater with longer duration (relative risk after five or more years of use, 1.53). Cline et al.¹³ also observed that a combined estrogen-progestin regimen markedly increased breast-cell proliferation in postmenopausal cynomolgus monkeys.

The only apparent anomaly in these generally consistent results is related to coronary heart disease. The WHI, a primary-prevention trial of postmenopausal hormones (oral conjugated estrogen and continuous medroxyprogesterone acetate),¹ found that the rate of coronary heart disease was 29 percent higher among women assigned to combined therapy than among those assigned to placebo. Earlier, the Heart and Estrogen/Progestin Replacement Study (HERS)² found that women with established coronary disease who were assigned to the use of hormones (oral conjugated estrogen and continuous medroxyprogesterone acetate) had rates of recurrent coronary events similar to those among women given placebo. Yet substantial data from ob-

Table 1. Potential Explanations for Discordant Findings from Randomized Trials and Observational Studies Regarding Postmenopausal Hormone Therapy and Coronary Heart Disease.

Methodologic differences
Confounding ("healthy user") bias
Compliance bias
Incomplete capture of early clinical events
Biologic differences
Hormone regimen (formulation and dose)
Characteristics of study population (endogenous estrogen level, time since menopause, and stage of atherosclerosis)

Table 2. Results from Observational Studies of Combined Hormone Therapy and from the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study.*

Disease	Women's Health Initiative	Heart and Estrogen/ Progestin Replacement Study	Observational Studies of Estrogen with Progestin
	<i>relative risk (95% confidence interval)</i>		
Breast cancer <5 yr	1.26 (1.00–1.59)	1.30 (0.77–2.19)	1.15 ⁷
≥5 yr			1.53 ⁷
Colorectal cancer	0.63 (0.43–0.92)	NA	0.66 (0.59–0.74) ^{8†}
Hip fracture	0.66 (0.45–0.98)	1.10 (0.49–2.50)	0.75 (0.68–0.84) ^{9†}
Stroke	1.41 (1.07–1.85)	1.2 (1.0–1.4) [‡]	1.45 (1.10–1.92) ¹⁰
Pulmonary embolism	2.13 (1.39–3.25)	2.8 (0.9–8.7)	2.1 (1.2–3.8) ^{11†}
Coronary heart disease	1.29 (1.02–1.63)	0.99 (0.80–1.22)	0.61 (0.45–0.82) ¹²

* Relative risks are for the women receiving hormone-replacement therapy as compared with those not receiving hormone-replacement therapy. Confidence intervals are nominal. NA denotes not available.

† Estimates are for any hormone use, since there were insufficient data for estrogen plus progestin.

‡ Relative risk is for the combined risk of fatal and nonfatal stroke.

servational studies of hormone therapy have indicated that it protects against coronary heart disease. Although most of these studies involved the use of estrogen alone, limited data from observational studies of combined estrogen–progestin therapy also suggested protection against coronary heart disease; studies of combined therapy, however, have assessed predominantly cyclic regimens.

METHODOLOGIC ISSUES

CONFOUNDING BIAS, OR “HEALTHY USER” EFFECT

Confounding bias occurs when there is a failure to control fully for lifestyle or health-related factors that may differ in users and nonusers of hormones. In observational studies, women who choose to take hormones are generally healthier than women who choose not to take hormones, and this imbalance could lead to both an overestimate of protective effects and an underestimate of risks associated with postmenopausal hormone therapy. Yet the remarkable consistency of the trial data and the observational data regarding most benefits and risks of hormone therapy (Table 2) would suggest that there is little confounding in studies of the relations between hormone therapy and cancer, osteoporosis, stroke, and venous thromboembolism. Stroke, in particular, has a relation to socioeconomic status similar to that of heart disease and is preventable through many similar lifestyle and health practices.

Still, no observational study can eliminate confounding, and a recent report¹⁵ suggested that inadequate control for socioeconomic status could be an important limitation in observational studies of hormone therapy and coronary heart disease. In a meta-analysis,¹⁵ the authors noted that three studies^{16–18} that controlled for level of education or occupation found no overall protection against coronary heart disease by hormone therapy. However, each of these studies had reported that such adjustment had little effect on results, thus reducing the possibility that control for socioeconomic status was a decisive factor in their null findings. Furthermore, other studies have adjusted for socioeconomic status to the same extent as those included in the meta-analysis and still found a decreased risk of coronary disease among hormone users. These include, for example, the Nurses' Health Study,¹⁰ which controlled for educational level and occupation by including only registered nurses, and the Leisure World study,¹⁹ which adjusted for income by recruiting exclusively from a middle-class retirement community. In the Nurses' Health Study, additional control for husband's educational level, a strong marker of socioeconomic status, did not substantially change the results. Nonetheless, it is possible that coronary heart disease is particularly susceptible to confounding (more so than other conditions), and such bias in the observational data cannot be ruled out.

COMPLIANCE BIAS

Compliance bias is a type of confounding that occurs because women who adhere to hormone therapy also tend to adhere to other protective types of behavior (both measured and unmeasured). Randomized trials focused on coronary heart disease have found that persons who comply with placebo use have substantially lower rates of heart disease than those who do not comply with the use of placebo or active medication.²⁰ The hormone users in observational studies are compliant users of medication and may be more likely to take other agents (such as antihypertensive agents or cholesterol-lowering medications) or to participate in other activities (such as blood-pressure and cholesterol screening) that protect against coronary heart disease. Yet compliance with the use of a medication in a blinded clinical trial may not be equivalent to, or representative of, compliance with the use of a chosen or prescribed medication in an observational setting. Also, if compliance with healthful types of behavior explained the decreased risk of coronary disease associated with hormone use in observational studies, such compliance should have had a similar effect on the results with regard to stroke, but stroke was not less common among hormone users in most observational studies. Nonetheless, compliance bias could plausibly explain part of the reduction in the risk of coronary heart disease with hormone use, and further exploration of this issue is warranted.

INCOMPLETE CAPTURE OF EARLY CLINICAL EVENTS

Observational cohorts are well suited to the examination of long-term exposure. For example, almost 30 percent of women in the Nurses' Health Study have used hormones for 10 to 20 years; similarly, the Kaiser Permanente study²¹ included only women who had been taking hormones for at least five years. The average follow-up in the WHI and HERS was relatively short (about five to seven years), and even that duration of follow-up entails tremendous costs. Thus, trials are unlikely to provide information on women who have been taking hormones for 10 or more years — a practice that had become increasingly common (and is critical to address, since continuous use of hormones would be necessary to maintain hormonal effects on bone density).

In contrast, an important disadvantage of many prospective cohort studies is their limited ability to identify clinical events that occur early after the ini-

tiation of therapy. Most such studies collect information on hormone use only at base line; thus, any immediate increase in the risk of coronary heart disease (as noted in both the WHI and HERS) would not be detected, since new users are usually not specifically enrolled and would constitute a minority of the study subjects. (This is less of a problem in case-control studies; two^{16,17} of the three observational investigations discussed above that found no relation between hormone use and coronary heart disease had case-control designs.) In the Nurses' Health Study, one of the few prospective investigations that regularly updates data on hormone use, information is collected at two-year intervals.

This design would not capture information on women who both initiated hormone use and had a myocardial infarction within the same two-year time period. In fact, such women would be considered to be nonusers of hormones — a classification that would lead to a false elevation of the rate of coronary heart disease in “nonusers” and a possible overestimate of cardioprotection associated with hormone use. Indeed, the Nurses' Health Study reported an inverse relation between short-term hormone therapy and primary prevention of coronary heart disease¹⁰ and, on the basis of only eight cases, found a moderate but nonsignificant increase in the rate of recurrent coronary events among short-term users.²²

Although such a problem in identifying early clinical events is not an issue in all prospective studies (the Group Health Cooperative,²³ for example, used continually updated pharmacy records and reported a substantial short-term increase in recurrent coronary events with hormone use), it is a major limitation of many prospective studies and probably explains some of the discrepancies in the findings regarding heart disease in analyses of both primary and secondary prevention. This limitation is likely to be an important reason why most of these studies failed to predict the early increase in the risk of coronary heart disease found in the WHI and HERS.

Could such difficulty in identifying early clinical events be more important in the case of coronary heart disease than it is for other end points? In both the WHI and HERS, the increases in the risk of coronary disease associated with hormone therapy occurred predominantly on initiation (in WHI, the relative risk of coronary heart disease was 1.78 in year 1, as compared with 1.29 overall). For most other diseases, however, the elevation in risk began later (for stroke, the relative risk associated with hormone

use was 0.95 in year 1 and 1.43 overall; for breast cancer, the relative risk was 0.62 in year 1 and 1.26 overall) or persisted throughout follow-up (the relative risk of deep venous thrombosis was 3.60, 2.26, 1.67, 1.84, and 2.49 for years 1, 2, 3, 4, and 5, respectively). Thus, the inability to capture short-term effects of hormone therapy could be uniquely problematic for the study of coronary heart disease.

BIOLOGIC DIFFERENCES

Although methodologic issues are clearly important, they are unlikely to explain fully the divergent results of observational studies and clinical trials with regard to coronary disease. Thus, it is also important to consider biologic explanations. Data from earlier trials investigating hormone therapy and intermediate markers of coronary heart disease in women and in nonhuman primates indicated substantial benefits (e.g., improved lipid profile and enhanced endothelium-dependent vasodilation), although they also suggested some adverse effects (e.g., higher levels of certain inflammatory markers and coagulation factors).²⁴ It remains unknown exactly which of these (or other) biologic mechanisms are most important in predicting the risk of clinical coronary events. Some recent data suggest that the level of matrix metalloproteinase, which has been implicated in plaque rupture, may be increased by hormone therapy,²⁵ and this is a new area of active investigation. Indeed, there are several biologic differences between the trials and observational studies in terms of both the treatment regimens and the populations included, although most hypotheses about biologic differences are largely unexplored and require further attention.

HORMONE REGIMEN

The observational studies and the randomized trials may be answering different questions. One possible distinction is the regimen of hormones used. In observational studies, most women used estrogen alone (reflecting secular trends). The few investigations of combined therapy with estrogen and a progestin (including the Nurses' Health Study) have reported protection against coronary heart disease,^{10,11} although even in the large Nurses' Health Study, only a small percentage of users of combination hormone regimens took progestins on a daily basis — most took these agents on a cyclical basis (10 to 14 days per month). In contrast, both HERS and the WHI studied daily therapy with

a combination of estrogen and a progestin (Prempro, Wyeth–Ayerst). In clinical studies, the addition of medroxyprogesterone acetate (cyclically or continuously) to estrogen diminishes, although it does not eliminate, the increases in high-density lipoprotein caused by the use of estrogen alone, whereas the use of micronized progesterone in combination with estrogen maintains lipid benefits.²⁶ In contrast, all these hormonal formulations increase levels of C-reactive protein,²⁷ an inflammatory marker that predicts the development of coronary heart disease.²⁸ Thus, one implication of the trial data may be that we need further research on different hormone formulations and different doses of hormones.

CHARACTERISTICS OF THE POPULATIONS

Limited evidence suggests that the effects of hormones may differ in women with different clinical characteristics. For example, in contrast to women who are randomly assigned to hormone treatment in a clinical trial, women who choose to take hormones for menopausal symptoms or osteoporosis (i.e., the majority of women in observational studies) tend to be thinner and to have lower levels of endogenous estrogen; thus, they may constitute a group that benefits uniquely from hormone use. Body-mass index (the weight in kilograms divided by the square of the height in meters) is the strongest marker of endogenous estrogen in postmenopausal women that has been identified. Most studies have limited power to examine subgroups; however, in a very large cohort of 290,827 postmenopausal women,²⁹ the coronary benefits of hormone therapy exclusively affected women with a lower body-mass index. The mean body-mass index in the WHI was 28.5, and that in the Nurses' Health Study was 24.3.

In addition, a woman's age and the number of years since menopause are potential factors modifying the influence of hormones on coronary heart disease. By 35 years of age, women in the United States usually have only fatty streaks in their coronary arteries and minimal atherosclerotic plaques³⁰; the following decade (45 to 55 years of age) is a time of active progression of atherosclerotic lesions in the coronary arteries.³¹ By the time women are 65 years of age, on average, these lesions begin to develop complications.³² In the later stages of atherosclerosis, the prothrombotic or plaque-destabilizing effects of hormone therapy may predominate. It is possible that hormone therapy could be bene-

ficial in younger women, before plaque complications set in, but may not inhibit progression from complicated plaques to coronary events in older women.

In women with established cardiovascular disease participating in the Cardiovascular Health Study,³³ the flow-mediated vasodilator response (a measure of endothelial function) was equivalent among women who used hormones and those who did not. Among women without cardiovascular disease or major risk factors, hormone users had a response that was 40 percent better than that of nonusers. The Estrogen Replacement and Atherosclerosis trial,³⁴ a randomized trial involving women with documented coronary disease, reported no effect of estrogen alone or of estrogen combined with progestin on the diameter of coronary arteries. Yet in the Estrogen in the Prevention of Atherosclerosis Trial,³⁵ in which somewhat younger women without clinical cardiovascular disease were randomly assigned to estrogen alone or placebo, the average rate of progression of subclinical carotid atherosclerosis was slower in women assigned to estrogen.

Support for this hypothesis comes from randomized studies of postmenopausal, cynomolgus monkeys. Conjugated estrogen had no effect on the extent of coronary-artery plaque in monkeys assigned to estrogen alone or to estrogen combined with medroxyprogesterone acetate beginning two years (approximately six human years) after oophorectomy and substantially after the establishment of atherosclerosis. However, hormone treatment resulted in a 50 percent reduction in the extent of plaque when given to younger monkeys immediately after oophorectomy, during the early stages of atherosclerosis.³⁶

In the Nurses' Health Study, women ranged in age from 30 to 55 years at enrollment, and approximately 80 percent began to use hormones within two years after menopause. Although analyses limited to older women found protection against coronary heart disease,³⁷ most older women had used hormones for a long time, beginning at menopause. In contrast, the mean age of participants was 63 years in the WHI and 67 years in HERS; thus, these women had generally been postmenopausal for at least 10 years at the time of enrollment. Although the WHI investigators reported no protection against coronary heart disease among women 50 to 59 years of age (who accounted for one third of the study population), even in this subgroup, a substan-

tial number of subjects would have been assigned to hormone treatment at least six years after menopause. Moreover, few of these younger women had coronary events; thus, this study had a limited ability to detect such effects. There will probably never be a large-scale trial involving women who have just reached menopause, since the expense incurred for enrolling sufficient numbers of young women may be prohibitive.

CONCLUSIONS

There are numerous plausible explanations for the divergent findings with respect to coronary heart disease from clinical trials of hormone therapy and observational studies. Some discrepancies are certainly the result of methodologic differences between the study designs; the observational data could be influenced by confounding bias, compliance bias, and in particular, a restricted ability to detect short-term effects. Other explanations may be biologic and related to differences in the treatment regimens and in the subjects. But existing trials have limited ability to investigate the wide variety of hormone treatments available or to study effects in younger women who have just reached menopause — women who must make an important decision about whether to begin hormone therapy.

The clearest message from these studies is that we have much to learn about women's health and hormone use. Overall, however, given the current evidence, hormone therapy should not be initiated or continued for the purpose of preventing cardiovascular disease. Furthermore, we do not believe^{10,24} that long-term use (five years or more) of combined hormones should be recommended for women of any age for the prevention of chronic disease. The established increases in the risks of breast cancer, venous thromboembolism, and stroke are too high a price to pay.

Dr. Grodstein reports having received honorariums from Schering-Plough for consulting and speaker's fees from Novartis, Orion Pharma, and Pfizer. Dr. Clarkson reports having received honorariums from Solvay and Organon for consulting and speaker's fees from Schering Canada, Organon, Pfizer, and Wyeth.

We are indebted to Drs. Graham Colditz, Susan Hankinson, David Hunter, Frank Speizer, Meir Stampfer, and Walter Willett for their helpful and insightful comments.

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